

hydrogen attached to a tertiary carbon atom is not replaceable by sodium in liquid ammonia unless at least two phenyl groups are attached to the same carbon. Hydrogen might also be evolved from side chains attached to the longer peptide chains or from diketopiperazines. We regard the variation in acidity as due to the nature of the starting material, and to the conditions of the digestion. We think of both proteins and peptones as being built up of peptides and diketopiperazines with the peptones containing a relatively large amount of diketopiperazines.

### Summary

1. A study of the reaction of sodium in liquid ammonia with certain peptones has been made.

2. Peptones are acidic in liquid ammonia, and liberate hydrogen when sodium is added to them.

3. Peptones are more acidic in liquid ammonia than diketopiperazine, but less acidic than proteins or amino acids.

4. Silk peptones prepared by digesting silk fibroin for ten days pass through a minimum acidity on the second and third days.

5. Peptones are more closely related to diketopiperazine than are proteins in their acid reactions in liquid ammonia.

6. Peptones react in liquid ammonia as if they contained relatively more diketopiperazines than do proteins.

CHICAGO, ILLINOIS

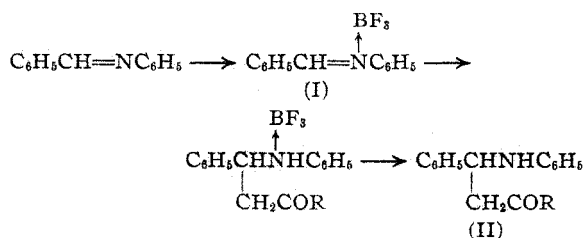
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

## Reactions of Anils. II. Addition of Methyl Ketones to Benzalaniline in the Presence of Boron Fluoride

BY H. R. SNYDER, H. A. KORNBERG AND J. R. ROMIG

In connection with a study of the reactions of anils,<sup>1</sup> it became desirable to effect the addition of methyl ketones to these substances. The reaction has been known for several years,<sup>2</sup> but in many cases it is a very slow process. Boron fluoride would be expected<sup>3</sup> to combine with an anil to produce the linkage  $\text{>C=N} \rightarrow \text{BF}_3$ , in which the double bond must be highly polarized because of the charge on the nitrogen atom. As a consequence of the increased polarization the complex should undergo addition reactions more readily than the anil. These predictions now have been realized. The coordination compound (I) is obtained readily and its rapid reaction with methyl ketones affords a convenient method of preparing amino ketones corresponding to (II).



**Procedure. Preparation of Benzalaniline-Boron Fluoride.**—To a solution of 2.86 g. of benzalaniline in 155 cc. of dry ether was added 2 cc. of boron fluoride etherate. The precipitate which appeared was separated; analysis showed it to be high in boron. The mother liquor, after standing for several hours in a closed flask, deposited yellow needles, m. p. 135–145° (dec.). The product was analyzed for boron by the hydrogen peroxide oxidation method of Snyder, Kuck and Johnson.<sup>4</sup>

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{11}\text{NBF}_3$ : B, 4.35. Found: B, 4.44.

**Addition of Methyl Ketones to Benzalaniline-Boron Fluoride.**—One and one-half grams of the coordination compound was dissolved in 25 cc. of acetone. The solution warmed slightly. After a few minutes water was added and the mixture was cooled. The colorless needles of 1-anilino-1-phenylbutan-3-one were collected and recrystallized three times from dilute alcohol; yield, 0.5 g., m. p. 87–88°.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{17}\text{ON}$ : N, 5.86; mol. wt., 239. Found: N, 5.86, 5.90; mol. wt., 251.

Substitution of ethyl methyl ketone for acetone gave 1-anilino-1-phenylpentan-3-one.<sup>2</sup> When the experiments were repeated with benzalaniline instead of the boron fluoride complex the anil was recovered.

For the preparation of amino ketones by this method the isolation of the coordination compound (I) is unnecessary. The reaction is effected more conveniently by adding boron fluoride etherate to a solution of the anil in an excess of the

(1) Snyder, Levin and Wiley, *THIS JOURNAL*, **60**, 2025 (1938).

(2) Mayer, *Bull. soc. chim.*, [3] **31**, 953, 985 (1904); [3] **33**, 157, 498 (1905); [4] **19**, 452 (1916).

(3) Kraus and Brown, *THIS JOURNAL*, **51**, 2690 (1929).

(4) Snyder, Kuck and Johnson, *THIS JOURNAL*, **60**, 110 (1938).

TABLE I  
 ADDITION OF KETONES TO BENZALANILINE-BORON FLUORIDE

No.	Ketone added <sup>a</sup>	No. of recrystallizations from	Amino ketone, RCOCH <sub>2</sub> CH(C <sub>6</sub> H <sub>5</sub> )NHC <sub>6</sub> H <sub>5</sub>					
			M. p., °C.	Yield, %	Molecular formula	Calcd.	Nitrogen, % Found	
1	Acetone	1, ligroin <sup>b</sup>	88-89	67	C <sub>16</sub> H <sub>17</sub> ON	5.86	5.86	5.90
2	Ethyl methyl ketone	1, ligroin <sup>b</sup>	120-121	66	Ref. 2			
3	Isobutyl methyl ketone	2, ligroin	80-81	61	C <sub>19</sub> H <sub>23</sub> ON	4.98	4.99	5.03
4	<i>n</i> -Amyl methyl ketone	2, ligroin	78-79	38	C <sub>18</sub> H <sub>25</sub> ON	4.75	4.71	4.85
5	4-Methyl-2-hexanone	2, ligroin						
		2, aq. MeOH	72-73	38	C <sub>20</sub> H <sub>25</sub> ON	4.75	4.81	4.83
6	Benzylacetone	4, ethanol	98-99.5	26	C <sub>23</sub> H <sub>23</sub> ON	4.26	4.15	4.09
7	Pinacolone	1, ethanol	148-149	71	C <sub>19</sub> H <sub>23</sub> ON	4.98	4.94	5.16
8	Cyclopentanone <sup>c</sup>	2, aq. MeOH						
		2, aq. acetone	163-164	42	C <sub>18</sub> H <sub>19</sub> ON	5.28	5.25	5.18
9	Acetophenone	3, aq. MeOH	166-167 <sup>d</sup>	62	Ref. 2			
10	Malonic ester <sup>e</sup>	3, aq. MeOH	98-99	6	Ref. 5			

<sup>a</sup> The procedure employed was as follows. A solution of 3.6 g. of benzaldehyde in four times the equivalent amount of the ketone was stirred in an ice-bath while 2.8 g. of boron fluoride etherate was added. After standing in the ice-bath for five minutes the solution was poured into 100 cc. of ice and water. The oil which separated soon solidified and was recrystallized as indicated in the second column. <sup>b</sup> These compounds were dissolved in 5% hydrochloric acid, filtered and reprecipitated by sodium bicarbonate prior to crystallization. <sup>c</sup> The solid obtained when cyclohexanone was used could not be purified. <sup>d</sup> Mayer<sup>2</sup> gives 173° as the melting point of this compound. <sup>e</sup> Equivalent amounts of malonic ester and benzaldehyde were used.

ketone. A summary of the results obtained by this method is given in the table. It should be mentioned that boron fluoride is not a true catalyst. For example, in variations of Expt. 9 of the table in which the molecular ratios of boron fluoride to benzaldehyde were 0.1, 0.32, 0.50 and 0.75, the yields of crude amino ketone were 0, 20, 38 and 68%, respectively.

Of the methyl ketones tested, all but acetone, mesityl oxide and benzyl methyl ketone gave the expected products. Whereas cyclopentanone reacted readily, cyclohexanone<sup>6</sup> gave only a trace of solid product and  $\alpha$ -tetralone gave none at all. Butyraldehyde, the only aldehyde tested, did not give a solid product. Of several compounds containing active methylene groups, only malonic ester gave an addition product. Methone and methyl cyanoacetate gave the benzal derivatives and dibenzoylmethane gave the enolic derivative, dibenzoylmethane boron difluoride.<sup>7</sup> From acetoacetic ester there was obtained only an intractable oil. The symmetrical ketones, diethyl ketone, di-*n*-butyl ketone and di-*n*-nonyl ketone, did not react under the conditions employed with methyl ketones. Benzyl cyanide, phenylacetylene, ethyl acetate and nitromethane likewise failed to give solid products.

(5) Goldstein, *Ber.*, **28**, 145 (1895).

(6) Pirrone describes the preparation of the amino ketone directly from cyclohexanone, benzaldehyde and aniline; *Gazz. chim. ital.*, **66**, 429 (1936).

(7) Morgan and Smith, *J. Chem. Soc.*, **125**, 1963 (1924).

Since the benzal derivatives of methone and methyl cyanoacetate were isolated, it seemed possible that the formation of amino ketones by this method might involve hydrolysis of the anil, reaction of the liberated aldehyde with the ketone, and addition of aniline to the unsaturated ketone so formed.<sup>8</sup> To test this possibility an experiment parallel to no. 1 was run, employing benzalacetone and aniline. Since none of the amino ketone was obtained, the alternate mechanism of direct addition of the ketone to the boron fluoride complex must be accepted.

In order to determine whether the addition of methyl ketones to benzaldehyde-boron fluoride is reversible, a small amount of 1-anilino-1-phenylbutan-3-one (II, R = CH<sub>3</sub>) was dissolved in an excess of pinacolone and treated with boron fluoride. In a similar experiment 1-anilino-1-phenyl-4,4-dimethylpentan-3-one (II, R = (CH<sub>3</sub>)<sub>2</sub>C) was treated with acetone and boron fluoride. The solutions were allowed to stand for one hour at room temperature. The starting material was recovered almost quantitatively from each, showing that the reaction is not reversible.

### Summary

Benzaldehyde and boron fluoride react in ether solution to give a coordination compound containing one molecule of each component.

The benzaldehyde-boron fluoride complex un-

(8) Tambor and Weld, *Ber.*, **31**, 352 (1898).

dergoes rapid addition of methyl ketones and cyclopentanone. The reaction affords a convenient method of preparation of certain  $\beta$ -amino ketones.

The addition of methyl ketones to benzalaniline in the presence of boron fluoride is not a reversible process.

URBANA, ILLINOIS

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### Reactions of Anils. III.<sup>1</sup> A New Type of Diels-Alder Reaction

BY H. R. SNYDER, R. B. HASBROUCK AND J. F. RICHARDSON

The reaction of maleic anhydride on compounds containing the structural unit  $\begin{array}{c} >C=C-C=N- \\ | \quad | \end{array}$  has now been examined in the course of a general study of the behavior in the Diels-Alder reaction of open-chain unsaturated systems containing nitrogen.<sup>2</sup> Since 2-ethyl-2-hexenal-aniline (I) is easily available, it was selected for the study.

2-Ethyl-2-hexenal-aniline reacts readily with maleic anhydride in boiling benzene. The product is a monobasic acid of the composition corresponding to one molecule of each reagent. This acid could not be reduced by sodium amalgam; hydrogen and platinum converted it into a dihydro derivative which could not be further hydrogenated. Both the original acid and the dihydro acids are extremely stable to hydrolysis, either with acids or bases. Fusion of the original acid with alkali brought about its decomposition into aniline and an acid of the composition  $C_{11}H_{14}O_2$ . Oxidation of the latter gave trimesic acid.

Since the condensation product is a monobasic acid, 1,4-addition of maleic anhydride to give the heterocyclic substance (II) is immediately excluded. An acid of the correct composition might be formed by addition to maleic anhydride, as has been observed in the case of certain pyrroles.<sup>3</sup> The primary addition product (III), by tautomerization and intramolecular amide formation, could then be transformed into the monobasic acid (IV). However, a substance having the formula (IV) should be reduced by sodium amalgam and should take up four hydrogen atoms on catalytic reduction. Furthermore, this formula does not account for the formation of an acid  $C_{11}H_{14}O_2$  which can be oxidized to trimesic acid.

The formation of the condensation product and all its properties can be accounted for readily on the basis of an aldimine-enamine tautomerism, involving a 1,5-shift of hydrogen, in the original anil (I  $\rightleftharpoons$  V). This transformation is not surprising, since the system  $\begin{array}{c} -CH_2-C=C-C=N- \\ | \quad | \quad | \end{array}$  is a vinylog of  $\begin{array}{c} -CH_2-C=N- \\ | \end{array}$  in which tautomerism is well known. Addition of maleic anhydride to the diene system of the tautomer gives the substance (VI) which, since it is at once an anhydride and a secondary amine, rearranges to form the bicyclic amido acid (VII).

A compound of the formula (VII) would be expected to resist the action of sodium amalgam and to give only a dihydro derivative on hydrogenation. Vigorous hydrolysis with alkali opens the amide ring to give the  $\beta$ -anilino acid salt (VIII). Loss of a molecule of aniline results in the formation of the dihydrobenzene derivative (IX). The latter is unstable; by expelling a molecule of potassium formate it is converted into the salt of 3,5-diethylbenzoic acid,  $C_{11}H_{14}O_2$ , (X). Oxidation of the latter gives trimesic acid (XI).

When this work was nearly complete, Bergmann<sup>4</sup> reported that cinnamalaniline (XIII) and maleic anhydride give only maleanilic acid and cinnamaldehyde. We have carefully reexamined this case; the results have been in harmony with those of Bergmann, except that under highly anhydrous conditions the yield of maleanilic acid was negligible, as might have been expected from the observation<sup>2</sup> that, in reactions of this kind, the first step is addition of water to the carbon-nitrogen double bond. The failure of cinnamalaniline to undergo condensation supports the formulation given for the reaction of 2-ethyl-2-hexenal-aniline; because the  $\epsilon$ -carbon atom is part of the benzene ring, cinnamalaniline is unable to undergo the initial tautomerization.

(1) For the preceding paper in this series see Snyder, Kornberg and Romig, *THIS JOURNAL*, **61**, 3556 (1939).

(2) Snyder, Levin and Wiley, *ibid.*, **60**, 2025 (1938).

(3) Diels and Alder *Ann.*, **486**, 211 (1931).

(4) Bergmann, *THIS JOURNAL*, **60**, 2811 (1938).