Anal. Calcd. for $C_{10}H_{13}ON_4Cl$: Cl, 14.8. Found: Cl, 15.0.

Of the two possible isomers, 2-chloro-4-dimethylaminobenzaldehyde had been prepared before[11] by an unambiguous synthesis; m. p. 82°. The 3-chloro-compound was synthesized by the following method and was found identical (mixed m. p.'s of the aldehydes and the semicarbazones) with the above substance.

o-Chlorodimethylaniline was prepared by heating *o*-chloroaniline (13 g.), methyl alcohol (20 cc.) and concd. sulfuric acid (1 cc.) for 16 hours at 160–170° (sealed tube), addition of alkali, extraction with ether and fractional distillation, b. p. 205–206°; yield 5.5 g.[12] This quantity was kept at room temperature for 24 hours, mixed with phosphorus oxychloride (5.5 g.) and N-methylformanilide (4.8 g.). Ice-water and alkali was added, the product extracted with ether, and the aldehyde transferred into aqueous bisulfite solution. The latter was treated with sodium carbonate and the aldehyde extracted with ether and isolated in form of its semicarbazone, m. p. 195–196°. Regenerated from this derivative, it had m. p. 74°; yield 0.6 g.

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[11] "Beilstein," Vol. XIV, p. 38.

[12] Heidlberg, *Ber.*, **20**, 149 (1887); Friedlaender, *Monatsh.*, **19**, 638 (1876).

REHOVOTH, ISRAEL RECEIVED MAY 26, 1950

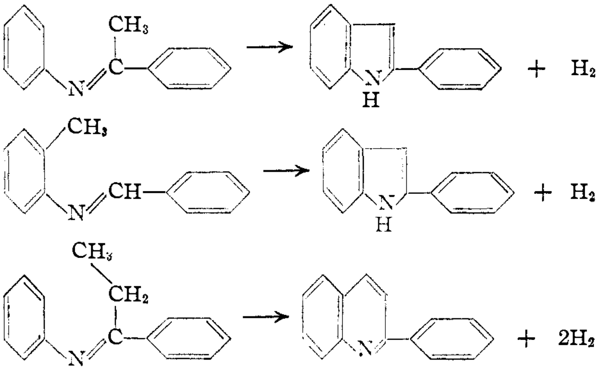
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

Catalytic Synthesis of Heterocycles. V.[1] Dehydrocyclization of Anils to Nitrogen Heterocycles

BY CORWIN HANSCH, DONALD G. CROSBY, MICHAEL SADOSKI, ALBERT LEO AND DOUGLAS PERCIVAL

The vapor-phase catalytic dehydrocyclization of six aromatic anils to indoles and quinolines, using a chromium–copper catalyst at temperatures of 500–575°, has been carried out. Conversions of anil to heterocycle range from 5–30% per pass. A mechanism for the reaction is suggested. An improved method for the preparation of acetophenone anils is described.

Three equations illustrate the general reactions which are described in this paper



This first work has been limited to the investigation of anils between aromatic amines and aromatic carbonyl compounds. It is planned to attempt to extend this reaction to anils derived from mixed aliphatic–aromatic amines and carbonyl compounds.

Some work on the pyrolysis of anils has been reported. Pictet and Ankersmit[2] showed that by passing benzalaniline through a tube at 800° about 2% phenanthridine was formed. Benzal-α-naphthylamine was shown to give some naphthacridine by pyrolysis[3] while benzal *o*-toluidine was found to give 30% 2-phenylindole on passing through a hot tube.[4] It was hoped that a study of these reactions with modern dehydrogenation catalysts might increase the scope and usefulness of such reactions.

Experimental

All experiments were carried out in a Pyrex catalyst tube in a continuous flow system. The apparatus and procedure used have been previously described.[5] In each run, 10 ml. of fresh catalyst was used. It was readied for use by reduction *in situ* with a slow stream of hydrogen for 0.5 hour at 150–200° and then for 1 hour a few degrees above the temperature at which the run was to be made. Those anils which were not liquid at room temperature were introduced in the catalyst in the molten state, being held this way by surrounding the introduction tube with a steam jacket.

Catalyst Preparations (I).—This chromium on alumina catalyst has been previously reported.[6] (2) Activated charcoal[7] was extracted in a Soxhlet extractor with constant boiling hydrochloric acid for 24 hours. The charcoal was then dried, covered with 48% hydrofluoric acid in a platinum dish and evaporated to dryness. This hydrofluoric acid treatment was repeated three times in all. The catalyst support was then extracted thoroughly with boiling distilled water and dried. Charcoal treated in this way contained less than 0.2% ash, while the original material contained about 16% ash, 12% of which was silica. Sixty-nine grams of this charcoal was added to a boiling solution of 108.3 g. of $Cr(NO_3)_3 \cdot 9H_2O$ and 2.64 g. of $Cu(NO_3)_2 . 3H_2O$ in 150 ml. of distilled water. The mixture was boiled several minutes, then filtered, washed with distilled water and dried at 110°. (3) In 50 ml. of water, 31.4 g. of $Cr(NO_3)_3 \cdot 9H_2O$ was dissolved. With this solution 30 g. of acid treated charcoal was treated as above. (4) In 20 ml. of water were dissolved 18 g. of $Cr(NO_3)_3 \cdot 9H_2O$ and 1.75 g. of $Cu(NO_3)_2 \cdot 3H_2O$. This solution was heated to boiling and 23 g. of acid treated charcoal added with good mixing. This material was dried at 110° without filtering.

Preparation of Ketone Anils.—The general method of Reddelien[8] was modified for the preparation of these compounds. The appropriate ketone and amine were refluxed in an inert solvent with a small amount of the zinc salt of the amine. The water formed was removed by means of a water trap and when no more water formed the mixture was cooled and filtered.

2-Acetothienone Anil.—2-Acetothienone (63 g.), aniline (75 g.) and 2 g. of aniline–zinc chloride were refluxed for 40 hours in 200 ml. of toluene. Distillation gave 65% yield, b.p. 136–137° (11 mm.), m.p. 70°.

Anal. Calcd. for $C_{12}H_{11}NS$: C, 71.60; H, 5.51. Found: C, 71.74; H, 5.86.

Propiophenone *o*-Tolylimide.—Propiophenone (100 g.), *o*-toluidine (80 g.) and 2 g. of *o*-toluidine–zinc chloride were

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[1] For the previous paper in this series see *Ind. Eng. Chem.*, **42**, 2114 (1950).

[2] Pictet and Ankersmit, *Ber.*, **22**, 3339 (1889); Pyle, *ibid.*, **60**, 287 (1927).

[3] Pictet and Ehrlich, *Ann.*, **266**, 155, 163 (1891).

[4] Pictet, *Ber.*, **19**, 1064 (1886).

[5] Hoog, Verheus and Zuiderweg, *Trans. Faraday Soc.*, **35**, 993 (1939).

[6] Hansch and Blondon, THIS JOURNAL, **70**, 1561 (1948).

[7] Type BP-6x8 obtained from the Pittsburgh Coke & Chemical Co.

[8] Reddelien, *Ber.*, **46**, 2715 (1913).

refluxed with 200 ml. of cumene for 24 hours. Distillation gave 60% yield, b.p. 153–155° (5 mm.), m.p. 37–38°.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.62. Found: C, 86.33; H, 7.92.

Aldehyde Anils.—These compounds were prepared by adding the hot aldehyde (150°) to an equimolar amount of *o*-toluidine at 150°. If the aldehyde was very pure, the reaction proceeded more rapidly if a drop of hydrochloric acid was added to the amine first. As soon as water ceased to evolve (a few minutes) the mixture was cooled and worked up.

Anisal *o*-Toluidine.—To 53 g. of hot *o*-toluidine was added 68 g. of hot anisaldehyde. Distillation gave 60% yield, b.p. 150° (2 mm.), m.p. 36–37°. Steinhart[9] reports m.p. 32° but gives no b.p.

Piperonal *o*-Toluidine.—To 52.5 g. of hot *o*-toluidine was added 75 g. of hot piperonal. After a few minutes the mixture was cooled and crystallized from ligroin, 85% yield, m.p. 104–106°. Recrystallization gave m.p. 105.5–106°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48. Found: C, 74.91; H, 5.48.

***p*-Dimethylaminobenzal *o*-Toluidine.**—To 21.4 g. of hot *o*-toluidine was added 30 g. of molten *p*-dimethylaminobenzaldehyde. The mixture was cooled after a few minutes and crystallized from ligroin giving 78% yield, m.p. 95–100°. Recrystallization gave m.p. 105–106°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.67; H, 7.60. Found: C, 80.92; H, 7.71.

2-Phenylindole.—The semi-solid condensates from the catalytic runs were crystallized from ligroin giving the yields indicated in Table I. This crude product melted at about 180°. Recrystallization gave a product m.p. 189°, picrate m.p. 127°. Madelung[10] reports m.p. 187° for 2-phenylindole and Bischler[11] reports m.p. 126° for its picrate. Mixed melting points with 2-phenylindole made from acetophenone phenylhydrazone showed no depression.

5-Methyl-2-phenylindole.—The semi-solid product from the catalytic runs was crystallized from ligroin, m.p. 213°; picrate m.p. 135°. Bischler[14] reports 213° for 5-methyl-2-phenylindole and m.p. 135° for its picrate.

2-Phenylquinoline.—The condensates from the catalytic runs were dissolved in petroleum ether and these solutions extracted several times with dilute hydrochloric acid. Neutralization of the acid extract precipitated 2-phenylquinoline, m.p. 85–86°; picrate m.p. 190.5–191.5°. Le Fevre and Pearson[12] report m.p. 85–86° for 2-phenylquinoline and m.p. 190–191° for its picrate.

2-(*p*-Methoxyphenyl)-indole.—The catalytic condensates were diluted with ligroin and the solids which separated were crystallized from benzene, m.p. 226–228°. Korczynski and Kierzek[13] report m.p. 228–229°.

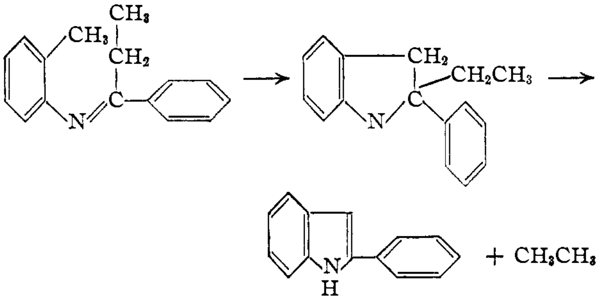
Discussion of Results

When this work was first undertaken, it was thought that possibly the formation of the anil and its subsequent dehydrocyclization might be carried out concurrently in the vapor phase by processing a mixture of the amine and carbonyl compound over the catalyst. A number of such runs were made and the results of some typical runs are shown in Table II. All of the runs gave low conversions and the gas evolved consisted of about 60% hydrogen the rest being saturated hydrocarbons. Thus the gas analysis indicated much more side reaction than in the dehydrogenation of the anil from acetophenone where in the best runs about 80% of the gas evolved was hydrogen.

2-Phenylindole.—Dehydrogenation of three different anils (acetophenone anil, benzal *o*-toluidine and propiophenone *o*-toluidine) resulted in the formation of 2-phenylindole. Of these reactions the one with benzal *o*-toluidine gave the best conversion. The reaction with this anil seems to be quite sensitive to temperature as is seen by comparing runs 133 and 196. In run 196 a large amount of low boiling material, toluene and benzonitrile,[4] was obtained. The gas evolution dropped off very rapidly due to poisoning of the catalyst.

Dehydrogenation of all of the anils investigated so far causes rather rapid poisoning of the catalysts. The rate of dehydrogenation as indicated by the gas evolution usually reached a relatively stable rate after about 10 minutes of the run. This rate gradually fell to a value of about $^1/_3$ after an hour. Thus runs larger than those indicated in Table I would not give as good yields unless a larger amount of catalyst were used. As one can see from comparing runs 132 and 134 slower space velocities result in slightly better yield. No doubt a detailed investigation would reveal more ideal conditions than these reported. Probably by using very slow space velocities with gaseous diluents one could achieve conversions of 50% or better per pass.

The formation of 2-phenylindole from propiophenone *o*-toluidine is quite interesting. At first glance one might expect either 8-methyl-2-phenylquinoline or 3-methyl-2-phenylquinoline. Only 2-phenylindole and starting material were identified in the condensate from this catalytic run. This affords a clew to the mechanism of cyclization. It seems reasonable to suggest that the methyl group adds across the imine double bond with the resulting intermediate decomposing to give the elements of ethane and 2-phenylindole



It seems unlikely that the ethyl group is split off before cyclization since propiophenone anil was not especially unstable and gave good conversions to 2-phenylquinoline.

2-Phenylquinoline.—The dehydrogenation of propiophenone anil might yield either 2-phenylquinoline or 3-methyl-2-phenylindole. In the two runs tried in this research, only the former compound could be identified. This is interesting in the light of the work of Padoa and Scagliarini.[14] They reported that the chief product obtained from passing tetrahydroquinoline over reduced nickel at 180° was skatole. On the basis of current ideas of the mechanism of dehydrocyclization[5,15] it seems reasonable to suppose that the formation of the 2-phenylquinoline would proceed through an intermediate dihydroquinoline. This could rearrange and dehydrogenate to give an indole or dehydro-

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[9] Steinhart, *Ann.*, **241**, 340 (1887).

[10] Madelung, *Ber.*, **45**, 1131 (1912).

[11] Bischler, *ibid.*, **25**, 2871 (1892).

[12] Le Fevre and Pearson, *J. Chem.Soc.*, 2807 (1932).

[13] Korczynski and Kierzek, *Gazz. chim. ital.*, **55**, 361 (1925).

[14] Padoa and Scagliarini, *Lincei*, **14**, 728 (1908).

[15] Pitkethly and Steiner, *Trans. Faraday Soc.*, **35**, 979 (1939).

TABLE I

DEHYDROCYCLIZATION OF ANILS[a]

Run No.	Reactant	Used, g.	Product	Conversion, %	S. V.[b]	Temp., °C.	Gas analysis, % H_2	Unsat.	Sat.
9	Acetophenone anil	36.5	2-Phenylindole	16.5	670	525	74	0	26
6	Acetophenone anil	39.0	2-Phenylindole	22.5	660	555	79	0	21
10	Acetophenone anil	39.0	2-Phenylindole	11.0	670	575	51	0	49
7[a]	Acetophenone anil	39.0	2-Phenylindole	8.0	660	550	44	0	66
8[a]	Acetophenone anil	39.0	2-Phenylindole	15.0	650	545	88	5	7
13	Acetophenone *p*-tolylimide	42.0	5-Methyl-2-phenylindole	7.0	610	550	13	0	87
15	Propiophenone anil	30.0	2-Phenylquinoline	20.0	650	510	54	0	46
14	Propiophenone anil	33.5	2-Phenylquinoline	14.5	615	540	52	0	48
18	Propiophenone *o*-toluidine	41.5	2-Phenylindole	14.0	555	550	53	0	47
132	Benzal *o*-toluidine	39.0	2-Phenylindole	23.0	530	525	86	2	12
133	Benzal *o*-toluidine	39.0	2-Phenylindole	31.0	530	550	86	2	12
196	Benzal *o*-toluidine	39.0	2-Phenylindole	5.0	690	575	88	0	12
134	Benzal *o*-toluidine	36.5	2-Phenylindole	28.0	228	525	87	0	13
135	Anisal *o*-toluidine	45.0	2-(*p*-Methoxyphenyl)-indole	7.0	520	525	40	0	60
63	Anisal *o*-toluidine	45.0	2-(*p*-Methoxyphenyl)-indole	9.0	600	500	79	1	20

[a] Catalyst 2 used in all runs except 7 and 8. Catalyst 3 used in run 7 and Catalyst 4 used in run 8. [b] S.V. is space velocity calculated as ml. gas/ml. cat./hr. at S.T.P.

genate to give a quinoline. The latter course is favored.

Substituted 2-Phenylindoles.—The results on two of these syntheses are reported in Table I. Acetophenone *p*-tolylimide was dehydrogenated to 5-methyl-2-phenylindole and anisal *o*-toluidine was converted to 2-(*p*-methoxyphenyl)-indole, both reactions giving low conversions. With anisal *o*-toluidine considerable charring occurred in the catalyst tube. Very little charring occurred with the acetophenone *p*-tolylimide although as the gas analysis indicates, considerable side reaction must have occurred since only 13% of the gas evolved was hydrogen.

Several attempts to dehydrogenate anils not reported in Table I were made. Piperonal *o*-toluidine, *p*-dimethylaminobenzal *o*-toluidine, 2-acetothienone anil and furfural *o*-toluidine were extensively decomposed when attempts were made to dehydrogenate them at temperatures from 475 to 550°. The gas evolved in these reactions was very low in hydrogen, about 10–15%. The acetothienone anil and the furfural *o*-toluidine were especially sensitive, and both charred very badly throughout the catalyst tube.

During the past few years many different types of catalysts for the dehydrocyclization of compounds containing oxygen, nitrogen and sulfur atoms to heterocycles have been investigated in this Laboratory. Of all those tried the most versatile catalyst is chromium–copper-on-charcoal (catalyst 2). A number of these catalysts have been prepared with different ratios of these metals. The amount of copper is not highly critical as can be seen by comparing run 8 with runs 6 and 9. A small amount of copper is important as can be seen by comparing runs 7 and 6. Recent work in this Laboratory has shown that catalyst 2 is the best catalyst investigated so far for the dehydrocyclization of *o*-ethylthiophenol to thianaphthene, *o*-ethylphenol to benzofuran, *o*-ethylaniline to indole and for the anils reported in this paper.

TABLE II

DEHYDROCYCLIZATION OF ANILINE AND ACETOPHENONE TO 2-PHENYLINDOLE

Run no.	Mixture[a] used, g.	Cat.	S. V.[b]	Temp., °C.	Conversion, %
1	40.5	1	1130	547	1.3
2	43.5	2	1890	545	6.5
4	43.0	2	1920	557	3.0

[a] These figures represent grams of an equimolar mixture of aniline and acetophenone. [b] Calculated as ml. vapor/ml. catalyst/hr. using an average molecular weight of aniline and acetophenone.

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