[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

Catalytic Synthesis of Heterocycles. VI. Dehydrocyclization of *o*-Alkylbenzenes to Indoles

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The dehydrocyclization of *o*-ethylaniline to indole and of *o*-isopropylaniline to skatole are discussed. Attempts to extend this reaction to the preparation of amino indoles were unsuccessful. A mechanism for the formation of indole, thianaphthene, and benzofuran by dehydrocyclization is suggested. Procedures for the synthesis of 2,4-diaminoethyl- and isopropylbenzenes are given. The ortho-para ratios for the nitration of ethyl- and isopropylbenzenes have been determined and compared with that previously reported for toluene.

In continuing our program[1,2] of developing catalytic methods for the synthesis of heterocycles it was decided to investigate the method reported for indole in a recent patent by Gresham and Bruner.[3] They reported the dehydrocyclization of *o*-ethylaniline to indole by means of a titania gel catalyst at temperatures of 550 to 750°. These investigators make no mention of attempts to extend this unique synthesis to other indoles. Although previous work indicated that indoles could be obtained by the dehydrocyclization of N-ethylaniline,[4] N-methyl-*o*-toluidine[5] or N,N-dimethyl-*o*-toluidine[6] the approach of Gresham and Bruner was selected so that comparison could be made with the procedures developed for benzofurans and thianaphthenes.[2,7] It was our hope that the method could be extended to other indoles, in particular the amino indoles in which the amine group is attached to the benzene ring of the indole nucleus. Previous unpublished results indicate that the presence of an amine group (para to the alkyl group) on the ring of *o*-ethylthiophenol greatly increases the tendency of the thiophenol to undergo dehydrocyclization to the aminothianaphthene according to the procedure developed for thianaphthene itself.[7]

TABLE I[a]

DEHYDROCYCLIZATION OF *o*-ETHYLANILINE TO INDOLE

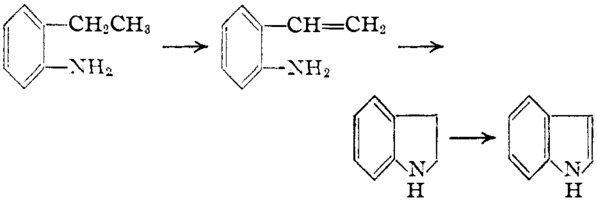
Run	Used, g.	Conversion, %	Temp., °C.	S.V.[b]	Gas analyses, % Unsatd.	H₂	Satd.	Total ml. gas evolved[c]
1	37.7	Trace	560	911	0.9	89.0	10.1	2990
2	39.0	Trace	570	902	3.6	87.7	8.7	3150
3	37.5	1.4	635	834	1.4	78.3	20.3	4630
4	22.0	17.6	650	1150	7.5	71.6	20.9	4810
5	21.3	10.2	650	611	1.0	79.0	20.0	4700
6	21.1	32.4	670	1120	0.6	74.9	24.5	4980

DEHYDROCYCLIZATION OF *o*-ISOPROPYLANILINE TO SKATOLE

Run	Used, g.	Skatole, %	Indole, %	Temp., °C.	S.V.[b]	Gas analyses, % Unsatd.	H₂	Satd.	Total ml. gas evolved[c]
7	41.0	1.6	8.7	625	980	1.5	74.8	23.7	6330
8	40.3	7.3	16.1	650	1000	2.9	59.4	37.7	8080

[a] Chromium-copper-on-charcoal, catalyst number 2, reference (1), used in all of these runs. [b] Space velocity is recorded here as ml. gas/ml. catalyst/hr. at N.T.P. [c] Measured at N.T.P.

In repeating Gresham and Bruner's work with *o*-ethylaniline, but using a previously reported chromium-copper-on-charcoal catalyst[1] it was found that at the optimum temperature of 670°, 32% conversion to indole could be obtained. Surprisingly little decomposition of aniline or indole occurred under these rather drastic conditions. The results are summarized in Table I. From runs 1 and 2, one can see that although considerable dehydrogenation occurred almost no cyclization to indole took place at 600° or below. This permits a rather easy method for the synthesis of *o*-aminostyrene. Even at 560°, 65% conversion of *o*-ethylaniline to aminostyrene occurred. This is of interest with respect to the mechanism of the dehydrocyclization. This evidence coupled with that previously reported[8,9,1] indicates that the following mechanism is highly probable



Using this same catalyst it was found that *o*-ethylphenol gave 10% conversion to benzofuran at 600° and that *o*-ethylthiophenol gave 35% conversion to thianaphthene at 450°. At lower temperatures each of these compounds also gave the corresponding styrenes. Thus the relative order of ease of cyclization of the three compounds is: SH > OH > NH_2.

In an attempt to test the hypothesis that cyclization involves transfer of a proton from the amino group to the α-carbon atom of aminostyrene several

TABLE II[a]

CYCLIZATION OF *o*-AMINOSTYRENE TO INDOLE

Used, g.	Cat.,[b] %	Conversion, %	Temp., °C.	Gas analyses, % Unsatd.	H₂	Satd.	Total ml. gas evolved[c]
18.7	5CaO	4.1	575	2.0	61.5	36.5	2060
22.5	2.5K_2O	2.9	560	2.7	76.3	21.0	2290
25.0	5KH_2PO_4	Trace	570	3.0	58.2	38.8	2350

[a] Space velocity of all runs 1000 ml. vapor/ml. cat./hr. at N.T.P. [b] These catalysts consisted of 5 ml. of the standard chromium-copper catalyst, plus 5 ml. of the catalyst listed in this column. [c] Measured at N.T.P.

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(1) C. Hansch, D. G. Crosby, M. Sadoski, A. Leo and D. Percival, THIS JOURNAL, **73**, 704 (1951).

(2) C. Hansch, C. Scott and H. Keller, *Ind. Eng. Chem.*, **42**, 2114 (1950).

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runs were made with base-promoted catalysts in the cyclization of this substance. The *o*-aminostyrene was prepared by dehydrogenation of *o*-ethylaniline and contained some of this material. The results are listed in Table II.

As can be seen from Table II, the basic oxides caused greater cyclization and also caused more decomposition as can be seen from the gas analyses. At temperatures above 600° decomposition was excessive. No doubt by a careful investigation of a number of bases and their ratio to the dehydrogenation catalyst yields better than those reported in Table I could be obtained. The straight chromium–copper catalyst resulted in trace conversions as did the acidic substance KH_2PO_4. It has long been known that metal oxides[10] are the most effective catalysts in the conversion of paraffins to aromatics. Part of the function of the oxide may well be to aid in cyclization as above by proton transfer.

Attempts to extend the reaction to skatole were none too successful. Although the cyclization took place at a slightly lower temperature, a high proportion of the skatole was cracked to give indole. As may be seen from the gas analysis from run 8, much greater decomposition occurred than with the corresponding ethyl compound.

Dehydrocyclization attempts with the 2,4-diaminoethyl- and isopropylbenzenes were completely unsuccessful because of excessive decomposition. At 600° and above, decomposition resulted in considerable charring, formation of large amounts of NH_3 and gaseous hydrocarbons. Attempts to isolate substances with the expected properties of the aminoindoles were fruitless.

It is unlikely that dehydrocyclization of *o*-alkylanilines will be of use for the synthesis of indoles other than indole itself. The required temperature for the reaction is so high that almost all groups with the possible exception of the methyl group would be cracked off either from the starting material or the product.

The ortho–para ratios for the nitration products of ethyl- and isopropylbenzene were determined and are compared below with that for toluene.[11] The value obtained for ethylbenzene agreed with that reported by Cline and Reid.[12] These values fall in the expected order, with the isopropyl group causing much greater steric hindrance than the ethyl group.

	o/p Ratio
Toluene	1.4
Ethylbenzene	1.1
Isopropylbenzene	0.35

Experimental

Processing Technique.—The apparatus was similar to that previously reported.[8] However, in the runs above 625° a catalyst tube made from Corning 172 glass was used instead of the usual Pyrex. In all experiments 10 ml. of catalyst was used preceded by about 10 ml. of quartz chips which served as preheater for the incoming vapors. Before use, the catalyst was reduced *in situ* with a slow stream of hydrogen for one-half hour at 150–200° and then for one hour a few degrees above that at which the reaction was to be run. The indole and skatole were isolated from the condensate by first extracting the unconverted aniline and aminostyrene with dilute hydrochloric acid and then steam distilling the residue to obtain the pure indole. The amount of indole present in the skatole was determined by repeated crystallization from water and alcohol.

Catalysts.—The procedure for the preparation of the chromium–copper-on-charcoal catalyst has been described. It is catalyst no. 2 reported by Hansch, *et al.*[1] The catalysts reported in Table II were prepared by adding acid-washed charcoal to a strong hot solution of $Ca(NO_3)_2$, KNO_3 or KH_2PO_4. The amount of salt adsorbed was determined by filtering off the catalyst after a few minutes, evaporating the filtrate to dryness and weighing the residue.

***o*- and *p*-Nitrocumenes.**—The following modification of the method reported by Sterling and Bogert[13] was found to give much higher yields. We were unable to repeat the yields indicated by them under the conditions they described. A mixture of 750 g. of concd. sulfuric acid and 550 g. of concd. nitric acid was stirred dropwise into 860 g. of cumene at 45°. This temperature was maintained by means of an ice-bath. The mixture was then stirred vigorously for two hours, the temperature being held within a few degrees of 45°. The nitration products were then separated, washed with water, 5% $NaHCO_3$ and again with water. After drying this solution over anhydrous magnesium sulfate it was distilled through a 30″ spinning band column (all distillations reported here were made with such a column) until the fractions gave a constant refractive index. *o*-Nitrocumene, b.p. 110.5° (13 mm.), $n^{25}D$ 1.5238. *p*-Nitrocumene, b.p. 131° (14 mm.), $n^{25}D$ 1.5350. The results of a number of runs are

Temperature of nitration, °C.	25	30	45
Nitration to mono nitro compounds, %	39	43	62
Ortho/para ratio	0.38	0.35	0.31

***o*-Isopropylaniline.**—*o*-Nitrocumene in an equal volume of methanol was reduced with Raney nickel catalyst. *o*-Isopropylaniline was obtained in 92% yield, b.p. 102° (14.5 mm.), $n^{25}D$ 1.5494. A b.p. of 217–220° has been reported.[14]

2,4-Dinitrocumene.—This compound was prepared by the nitration of cumene and also by the nitration of nitrocumene. A. A mixture of 262 g. of concd. nitric acid and 440 g. of concd. sulfuric acid was stirred dropwise into 120 g. of cumene at 80° and stirring continued for two hours. This was worked up as for nitrocumene; yield 43%, b.p. 142–143° (3 mm.), $n^{25}D$ 1.5528. Sterling[13] obtained some as a by-product in the preparation of nitrocumenes and reports b.p. 136° (2 mm.).

B. Into a mixture of 545 g. of concd. nitric acid and 800 g. of concd. sulfuric acid at 45° was stirred 253 g. of *p*-nitrocumene. Stirring was continued for two hours, the temperature being raised to 60°. The reaction mixture was worked-up as above; yield 96%.

2,4-Diaminocumene.—In 100-ml. of methanol was dissolved 80.6 g. of 2,4-dinitrocumene. This solution was hydrogenated over Raney nickel at 1300 lb. at 95–120° until no more hydrogen was taken up. Product was worked up as was aminocumene; 90% yield, b.p. 136–137° (2.5 mm.). On standing, the product crystallized, m.p. 31.5–32.5°. (All melting points reported here are corrected.) This amine was very rapidly oxidized by air, but could be stored under vacuum.

Anal. Calcd. for $C_9H_{14}N_2$: C, 72.00; H, 9.34. Found: C, 72.04; H, 9.24.

Hofmann[15] reports this compound having a m.p. of 47°. It seems likely that he had the impure hydrate of the diamine.

2,4-Diaminocumene Hydrate.—Crystallization of the diamine from aqueous ethanol gave a product m.p. 57.2–57.7°. When this material was dried in a vacuum over phosphorus pentoxide the original diamine, m.p. 30–31.5, was recovered.

Anal. Calcd. for $C_9H_{14}N_2 \cdot {}^1/_2H_2O$: C, 67.92; H, 9.45. Found: C, 68.35; H, 9.37.

2,4-Diacetylaminocumene.—Refluxing 2,4-diaminocumene with acetyl chloride for a few minutes gave a product

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[11] A. F. Holleman, *Chem. Revs.*, **1**, 187 (1925).

[12] E. L. Cline and E. E. Reid, THIS JOURNAL, **49**, 3153 (1927).

[13] E. C. Sterling and M. T. Bogert, *J. Org. Chem.*, **4**, 25 (1939).

[14] E. J. Constam and H. Goldschmidt, *Ber.*, **21**, 1157 (1888).

[15] A. W. Hofmann, *Compt. rend.*, **55**, 782 (1862).

which on crystallization from ethanol–water melted at 217.4–217.6°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69. Found: C, 67.09; H, 7.91.

2,4-Diaminocumene Dibenzoate.—The dibenzoyl derivative was prepared by the Schotten–Baumann procedure. The white product was crystallized from ethanol, m.p. 241.2–241.5°.

Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.14. Found: C, 77.30; H, 6.44.

2,4-Diaminocumene Dihydrochloride.—The diaminocumene was best stored as the hydrochloride which was stable toward air oxidation. This derivative was prepared by passing dry HCl into an ether solution of the amine and filtering the resulting precipitate; m.p. about 275° dec.

Anal. Calcd. for $C_9H_{16}N_2Cl_2$: C, 48.43; H, 7.18. Found: C, 48.02; H, 7.41.

2,4-Dinitroethylbenzene.—This substance was prepared according to the procedure of Borsche[16]; yield 56%, b.p. 126° (2 mm.), n^{25}_{D} 1.5655. On fractionation of the 2,4-dinitroethylbenzene it was found that the first fraction on cooling and standing yielded a considerable amount of a solid which after crystallization from methanol melted at 57–57.8°. Brady, Day and Allam[17] report 2,6-dinitroethylbenzene melts at 57.5°.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.08. Found: C, 48.71; H, 4.59.

2,4-Diaminoethylbenzene.—This substance was prepared according to the procedure used for diaminocumene; yield 86%, b.p. 127° (2 mm.), n^{25}_{D} 1.6088. 2,4-Diaminoethyl benzene has been previously reported by Weisweiller,[18] but he gave no physical constants.

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.59; H, 8.83. Found: C, 70.63; H, 9.29.

2,4-Diaminoethylbenzene Dibenzoate.—The dibenzoate was prepared by the Schotten–Baumann reaction. It was purified by crystallization from glacial acetic acid; m.p. 231.2–231.6°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.82. Found: C, 76.68; H, 6.24.

2,4-Diaminoethylbenzene Dihydrochloride.—The free diamine was very sensitive to air oxidation and was stored as the hydrochloride; m.p. about 270° dec.

Anal. Calcd. for $C_9H_{14}N_2Cl_2$: C, 45.93; H, 6.70. Found: C, 45.88; H, 7.03.

Acknowledgment.—This research was supported by the Office of Naval Research under contract NR-055-149. The carbon–hydrogen analyses reported in this paper were made by C. F. Geiger of Chaffey College, Ontario, California.

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(16) W. Borsche, *Ann.*, **386**, 365 (1919).

(17) O. L. Brady, J. N. E. Day and P. S. Allam, *J. Chem. Soc.*, 978 (1928).

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CLAREMONT, CALIF. RECEIVED DECEMBER 11, 1950

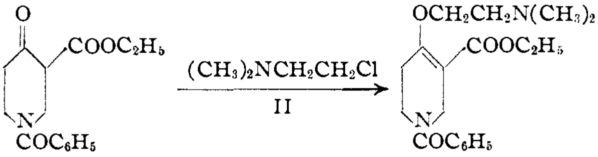
[CONTRIBUTION FROM HAVEMEYER LABORATORY, COLUMBIA UNIVERSITY]

The Alkylation of β-Ketoesters with β-Dimethylaminoethyl Chloride[1]

BY W. VON E. DOERING AND SARA JANE RHOADS[2]

β-Dimethylaminoethyl chloride reacts with sodio-1-benzoyl-3-carbethoxy-4-piperidone to give C-alkylation, with sodio- and potassio-2-carbethoxycyclohexanone to give the O- and C-alkylated products and with sodio-acetoacetic ester to give the C-alkylated product.

A hypothetical path for the synthesis of homomeroquinene[3] involves the alkylation of 1-benzoyl-3-carbethoxy-4-piperidone (I)[4] with a two carbon fragment convertible to a vinyl group.



I III

One fragment of this type, β-phenoxyethyl iodide, was found by Stork and McElvain[5] to be insufficiently reactive to alkylate I, although benzyl chloride and ethyl iodide reacted smoothly, the latter leading to a successful synthesis of cincholoipon. β-Dimethylaminoethyl chloride (II) seemed promising as a very reactive halide which is reported to give C-alkylation with acetoacetic ester[6] and with 2-carbethoxycyclohexanone[7] and is closely related to β-diethylaminoethyl chloride, a reagent that has been reported to give C-alkylation with acetoacetic ester[8] and 2-carbethoxycyclohexanone.[9]

In refluxing *t*-butyl alcohol, benzene, toluene or xylene, I reacts with II to give the product of O-alkylation, ethyl 1-benzoyl-4-(β-dimethylaminoethoxy) - 1,2,5,6 - tetrahydropyridine - 3 - carboxylate (III), instead of the expected C-alkylation product. The structural assignment depends primarily on the facts that III decolorizes bromine and potassium permanganate instantly, reacts with alcoholic hydrogen chloride to regenerate I and is hydrolyzed by aqueous hydrochloric acid to give carbon dioxide, benzoic acid, a small amount of 4-piperidone hydrochloride and β-dimethylaminoethanol (recovered as the benzoate).

Although a few examples of O-alkylation are known,[10,11,12] it is of interest to determine whether II characteristically reacts by O- rather than C-alkylation. With ethyl acetoacetate reaction is by C-alkylation (IV) as previously asserted but not proved.[6] Acid hydrolysis of the product gives 1-dimethylaminopentanone-4 (V) in good yield. On the other hand, 2-carbethoxycyclohexanone

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(1) Taken from a dissertation submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Vassie James Hill Fellow of the American Association of University Women, 1947–1948.

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(4) S. M. McElvain and G. Stork, *ibid.*, **68**, 1049 (1946).

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