Nitrotetrahydrocarbazoles: 8-chloro-6-nitro-3-methyl-tetrahydrocarbazole. Method A. A mixture of 5.6 g. (0.02 mole) of 4-methylcyclohexanone 2-chloro-4-nitrophenylhydrazone and 56 ml. of concd. hydrochloric acid (*d.* 1.18) was heated on water bath. The hydrazone dissolved to give a dark red solution. After a few minutes the solution attained turbidity and the nitrotetrahydrocarbazole started separating. After being heated for 3 hr. the product was filtered and crystallized from alcohol.

Method B. A mixture of 5.6 g. (0.02 mole) of the 2-chloro-4-nitrophenylhydrazone and 56 ml. of phosphoric acid (85%) was heated on water bath for an hour. The mixture was diluted and the product that separated was crystallized from alcohol.

Method C. A solution of 14 ml. of concd. sulfuric acid in 42 ml. of glacial acetic acid was mixed with 5.6 g. (0.02 mole) of the above hydrazone. The mixture was refluxed for 2 hr. After dilution the product was crystallized from alcohol.

Nitroindolenines: 7-nitro-2,3-3-trimethylindolenine. Method A. A mixture of 2.2 g. (0.01 mole) of 2-nitrophenylhydrazone of methyl isopropyl ketone and 22 ml. of concd. hydrochloric acid (*d.* 1.18) was heated for 3 hr. The nitroindolenine, being basic, remained in solution. Any suspended matter in the solution was removed by filtration. The filtrate was made basic and the nitroindolenine was extracted with benzene. The benzene layer was separated and dried. On evaporating the solvent, the residue was crystallized from dilute alcohol to afford the pure indolenine.

Method B: methylation of 7-nitro-2,3-dimethylindole. A solution of 3.5 g. (0.02 mole) of 7-nitro-2,3-dimethylindole in 30 ml. of methyl alcohol and 2.8 g. (0.02 mole) of methyl iodide was refluxed in the presence of 2.1 g. (0.02 mole) sodium acetate for 12 hr. The solvent was removed and the residue on crystallization from dilute alcohol gave the pure 7-nitro-2,3,3-trimethylindolenine.

Nitrotetrahydrocarbazolenines: 8-nitro-11-methyltetrahydrocarbazolenine. A mixture of 4.9 g. (0.02 mole) of 2-nitrophenylhydrazone of 2-methylcyclohexanone and either 49 ml. of concd. hydrochloric acid (*d.* 1.18) or 49 g. of sulfuric acid (20%) was heated on water bath. After some time the mixture became almost clear. The solution was filtered and the filtrate made basic. The nitro-11-methyltetrahydrocarbazolenine was extracted with ether. After removing ether the residue was crystallized from alcohol.

Nitroindoles, nitrotetrahydrocarbazoles, nitroindolenines, and nitrotetrahydrocarbazolenines prepared by one or more of the methods described above together with their characteristics are described in Table I, II, III, and IV.

SCHOOL OF CHEMISTRY
MEERUT COLLEGE
MEERUT, INDIA

Toluene Disproportionation[1]

A. SCHRIESHEIM

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Aromatic disproportionation reactions are well-known.[2,3] However, the kinetics and mechanism of these disproportionation reactions have been only recently investigated in detail.[3] These studies are mainly concerned with the disproportionation reactions of the higher alkyl benzenes, and little work is reported on toluene disproportionation. Recent literature indicates that at 0 to 20° toluene is relatively inert toward aluminum bromide–hydrogen bromide and may be used as a reaction medium for reactions of the higher alkyl benzenes.[4] At 50°, and over relatively long time periods, toluene forms benzene, and higher molecular weight materials over aluminum bromide hydrogen bromide.[5]

The present investigation explored the possibility of selectively converting toluene into benzene and xylenes at moderate temperatures over an aluminum bromide–hydrogen bromide catalyst. During the course of these studies, the sole production of *m*-xylene in the C_8 benzene fraction was noted. It was also found that the *m*-xylene isomerized to an equilibrium mixture of *o*-, *p*-, and *m*-isomers on prolonged heating at 110°. The purpose of this note is to present these data and to offer an explanation for the observations.

Product distributions for the toluene disproportionation reaction over aluminum bromide–hydrogen bromide are depicted in Fig. 1 and 2. At 80.6°, a selective reaction occurs and xylene and benzene are produced. At this temperature, *m*-xylene comprises the entire xylene fraction. After about 60% toluene conversion, a small amount of C_9 and C_{10} aromatics appears. The C_9 fraction is, within experimental error, essentially all mesitylene. If it is assumed that the reaction is approaching equilibrium, then this apparent equilibrium may be compared with that calculated by assuming a multiple series of reactions and is shown in Column A of Table I.

In Figure 2, the results of the experiments at 110° are shown. Again, a rapid reaction occurs; however, this reaction produces C_{10} aromatics in higher amounts than found at 80.6°. It is also apparent from Figure 2 that both the xylenes and the C_9 aromatics have maxima in their concentration values. In addition, the benzene values appear to go through a maximum. At this temperature, only the C_{10} aromatic fraction continuously increases, and at the end of 240 minutes, this fraction is far above its calculated equilibrium value.

As in the experiments at 80.6°, the xylene fraction at 110° at initially pure *m*-xylene. However, this xylene isomer undergoes an isomerization reaction that increases as the disproportionation reaction progresses, Fig. 3. The isomerization reaction reaches an apparent equilibrium and values for *m*-, *p*-, and *o*-xylene at this equilibrium are compared in Column B of Table I with cal-

(1) Presented at the 138th Meeting of the American Chemical Society, New York, September, 1960.

(2) D. V. Nightingale, *Chem. Revs.*, **25**, 329 (1939).

(3) K. L. Nelson and H. C. Brown, Chapter on Aromatic Substitution in Volume III of the *Chemistry of Petroleum Hydrocarbons* edited by Brooks, *et al.* Reinhold Pub. Corp., New York, N. Y., 1955.

(4) H. C. Brown and C. R. Smoot, *J. Am. Chem. Soc.*, **78**, 2175 (1956).

(5) K. S. Pitzer and D. W. Scott, *J. Am. Chem. Soc.*, **65**, 803 (1943).

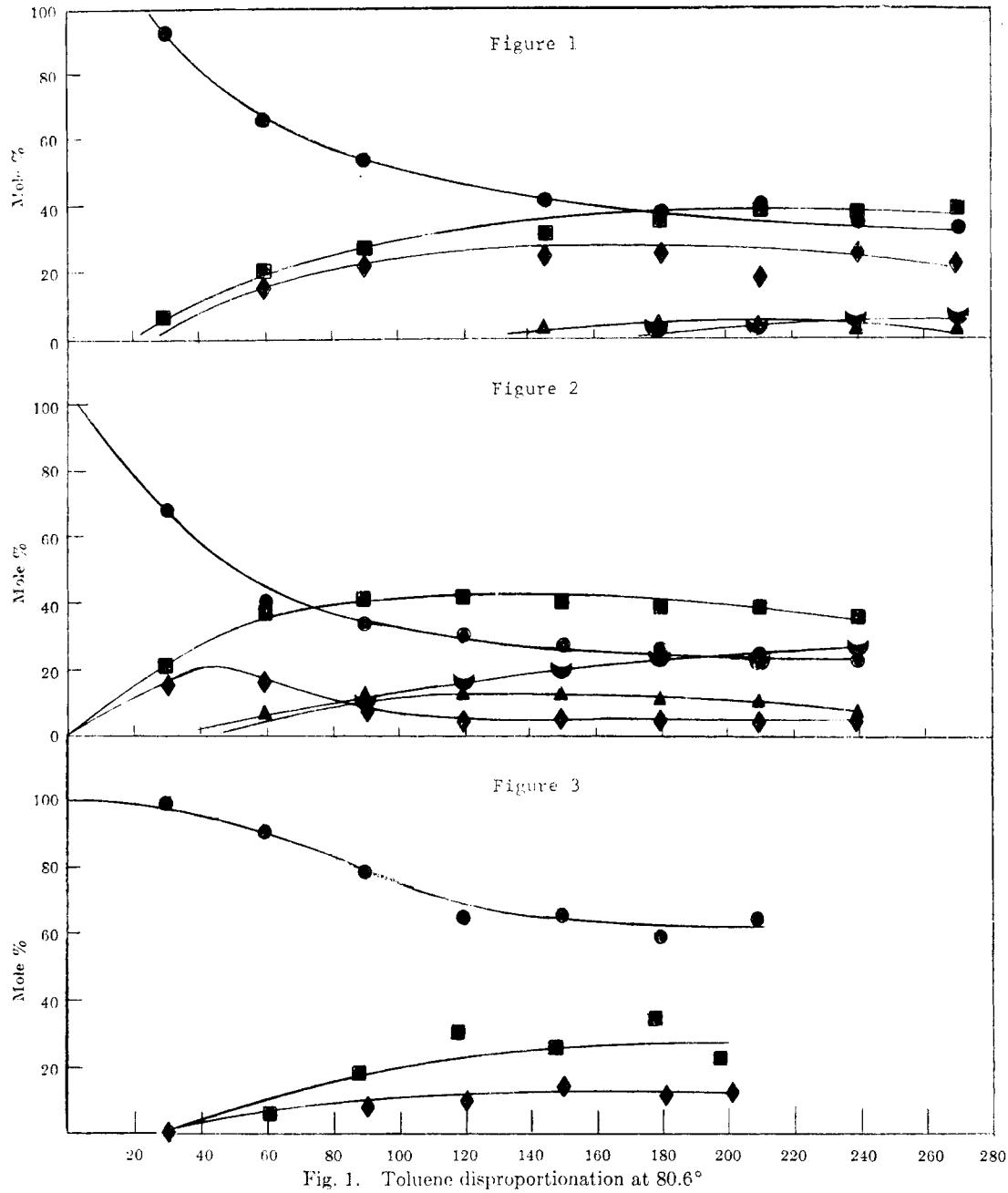


Fig. 1. Toluene disproportionation at 80.6°
Toluene ●; Benzene ■; Xylene ◆; Mesitylene ▲; C_{10} Aromatics ◡

Fig. 2. Toluene disproportionation at 110°
Toluene ●; Benzene ■; Xylene ◆; Mesitylene ▲; C_{10} Aromatics ◡

Fig. 3. Isomerization of *m*-xylene during course of toluene disproportionation at 110°
m-Xylene ●; *p*-Xylene ■; *o*-Xylene ◆

culated values and those found by McCaulay and Lien.[6]

The sole initial formation of *m*-xylene is interesting and may be rationalized as follows: It is well established that in hydrogen fluoride–boron trifluoride media, "complexing" conditions promote *meta* isomer formation, and this is probably due to stabilization of the *m*-xylene σ complex.[4,6] At complexing conditions, using hydrogen fluoride–boron trifluoride, *p*-xylene isomerizes to the *m*-isomer with an activation energy of 12.7 kcal./mole (0–30°).[6] While the activation energy of toluene disproportionation in the same system is not known, it must be appreciably higher since toluene is inert at temperatures where the xylenes isomerize. The activation energy of xylene disproportionation has been established in hydrogen fluoride–boron

(6) A. P. Lien and D. A. McCaulay, *J. Am. Chem. Soc.*, 75, 2407, 2411 (1953).

TABLE I

EQUILIBRIUM COMPOSITION

A Equilibrium Composition Starting with Toluene at 80°			B Xylene Isomer Equilibrium at 110°			
				Equil. Concn., Mole % in Liquid 110°		
Compound, Mole %	80.6° Calcd.[a]	Found	Isomer	Calcd.[b]	McCaulay & Lien[c]	Found
Benzene	30.0	38				
Toluene	44.0	34				
Xylenes	24.0	24	*o*-Xylene	18	19	15
C_9 Arom.	1.5	1	*m*-Xylene	58	60	61
C_{10} Arom.	0.5	3	*p*-Xylene	24	21	24

[a] The details of the method used to calculate these equilibrium percentages will be published within the year in *Journal of Chemical & Engineering Data*. S. H. Hastings and D. E. Nicholson of Esso Research and Engineering Company are the authors. [b] W. J. Taylor, D. D. Wagman, M. G. Williams, K. S. Pitzer, and F. B. Rossini, *J. Res. Nat. Bur. Stds.*, **37**, 95 (1946). [c] Ref. 6.

trifluoride as 23 kcal./mole (80–110°), and this probably represents a lower limit for the activation energy of the toluene disproportionation reaction. Thus, in hydrogen fluoride–boron trifluoride the difference in the activation energy for toluene disproportionation and xylene isomerization is about 10 kcal./mole over the temperature range 0–30°.[7]

An equation involving the relative rates of xylene isomerization and disproportionation may be simply derived (Eq. 1). Setting $E_a^2 - E_a^1$ equal to 10 kcal./mole, this equation indicates that at 100° the isomerization reaction will proceed at a rate that is $\geq 10^5$ times that of the disproportionation reaction.

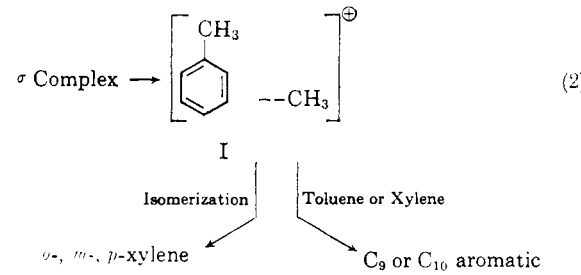
$$\frac{k_1}{k_2} = 10^{\frac{E_a^2 - E_a^1}{2.3\,RT}} \qquad (1)$$

where

k_1 = rate of *p*-xylene isomerization
k_2 = rate of *m*-xylene disproportionation
E_a^1 = activation energy for *p*-xylene isomerization
E_a^2 = activation energy for *m*-xylene disproportionation

At conditions where toluene disproportionates, therefore, the rate of *o*- or *p*-xylene isomerization to *m*-isomer might be immeasurably fast.[8] Practically, this suggests that at the experimental conditions used here, the extremely rapid isomerization of the xylene isomer precludes the identification of any isomer but *m*-xylene.

Also interpretable is the isomerization of *m*-xylene at 110° to an equilibrium mixture of the xylene isomers (Fig. 3). At the lower temperature, the *m*-xylene σ-complex is relatively stable and little reaction occurs during the time studies. However, at the higher temperature, enough energy is available to cause the *m*-xylene σ-complex to disproportionate and react with toluene forming C_9 and C_{10} aromatics. These reactions can be interpreted as occurring through the intermediate formation of π-complex transition states.[4,6] This π-transition state of xylene, I, however, has two reaction paths to follow. It may form the isomeric xylenes or product C_9 and C_{10} aromatics (Equation 2).



(2)

Since the C_9 and C_{10} aromatic fractions are more basic than the xylene fraction, it is reasonable to expect that the σ-complex of these higher molecular weight fractions with aluminum bromide–hydrogen bromide is thermodynamically most stable.[3] Therefore, as the C_9 and C_{10} aromatics are produced, aluminum bromide–hydrogen bromide is removed from the xylene fraction and Equation 3 is shifted to the right.

$$(\text{Xylene H}^{\oplus})\ Al_2Br_7^{\ominus} + (C_9\ \&\ C_{10})\ Ar \rightleftarrows \text{Xylene} + [(C_9\ \&\ C_{10}\ Ar)H]^{\oplus}\ Al_2Br_7^{\ominus} \qquad (3)$$

Due to this removal of aluminum bromide–hydrogen bromide the *m*-xylene σ-complex becomes less stable, and increasing amounts of *m*-xylene react to form the higher molecular weight species. In addition, as the complexing decreases, *m*-xylene isomerizes to form the equilibrium mixture of *o*-, *m*-, and *p*-xylenes.

EXPERIMENTAL

The experiments were performed in a 500-cc. thermostated reaction flask. The flask had three necks and was fitted with a stirrer, a reflux condenser, and a self-sealing neoprene diaphragm. A typical experiment was carried out in the following manner. One hundred and eighty-four grams of fractionated and dried toluene and 300 g. of redistilled aluminum bromide was placed into the reaction flask in a nitrogen atmosphere. Forty grams of dry hydrogen bromide

(7) D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1950).

(8) It is realized that the catalytic systems are different; however, there is little likelihood that there will be major differences in relative activation energies over the same temperature ranges.

was then bubbled into this mixture and the amount added was controlled by weighing the total assembly. After hydrogen bromide addition, the solution was visibly homogeneous. This mixture was then brought to reaction temperature, and the contents sampled as a function of time, by means of a hypodermic syringe inserted through the neoprene diaphragm. The sample was injected into ice water, worked up, and analyzed by a combination of infrared, mass spectrometric, and gas liquid partition chromatographic techniques. The analytical technique was estimated to be accurate to within ±5% at C_{10} aromatic values below about 15%. Above 15%, higher molecular weight materials were formed and these are included in the C_{10} aromatic values.

The outlet of the reflux condenser was connected to a gas collecting device. Only traces of gas were evolved during the experiments reported in this paper.

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LINDEN, N. J.

Heterocyclic Compounds. I. Synthesis of Some Isoquinoline Derivatives

R. J. SHAH, D. D. VAGHANI, AND J. R. MERCHANT

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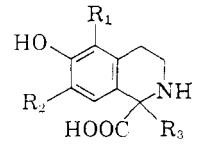
In connection with the synthesis of isoquinoline derivatives, we investigated the conditions of the Pictet-Spengler reaction[1] involving the condensation of β-phenethylamine derivatives with different α-keto acids and aldehydes.

The condensation of 2,3-dihydroxy-β-phenethylamine (B) with phenylpyruvic acid, α-keto-*n*-valeric acid and 3,4-dimethoxyphenylpyruvic acid in dioxane medium afforded the corresponding isoquinoline derivatives. With pyruvic acid or α-ketoglutaric acid, B failed to give any definite products.



I. R_1 = H; R_2 = OH; R_3 = C_3H_7
II. R_1 = H; R_2 = OH; R_3 = 3,4-$(OCH_3)_2CH_2C_6H_5$
III. R_1 = OH; R_2 = H; R_3 = $CH_2C_6H_5$
IV. R_1 = OH; R_2 = H; R_3 = C_3H_7
V. R_1 = OH; R_2 = H; R_3 = 3,4-$(OCH_3)_2CH_2C_6H_5$

The condensation of 3,4-dihydroxyphenylalanine (DOPA) with pyruvic, phenylpyruvic, or α-keto-*n*-valeric acid did not seem to occur.

With a view to synthesize the alkaloid calycotomine, isolated from the Australian plant Calycotome Spinosa Link (Leguminosae) by E. P. White,[2] the condensation of A with glycollic aldehyde was attempted under different conditions of *p*H and time. However, no pure product could be isolated in any case.

When the reaction of 3-hydroxy-4-methoxy-β-phenethylamine[3] with glycolic aldehyde was carried out in aqueous medium at *p*H 5 for seventy hours 1-hydroxymethyl-6-hydroxy-7-methoxy-1,2,-3,4-tetrahydroisoquinoline was obtained in poor yield. The latter on methylation with diazomethane afforded the dimethyl ether, *dl*-Calycotomine.

The latter has been synthesized also by A. Chatterjee[4] and by Battersby and co-workers.[5]

With DOPA the condensation of glycolic aldehyde was unsuccessful. It was, therefore, thought of interest to investigate the reaction of formaldehyde, acetaldehyde, and anisaldehyde with DOPA under different conditions. Only with formaldehyde, the desired 3 - carboxy - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline (VI) was obtained

Isoquinoline	*p*H	Time in Hours	M.P.	Yield, %	Formula	Found C, %	Found H, %	Found N, %	Calcd. C, %	Calcd. H, %	Calcd. N, %
I	6	96	226	55	$C_{13}H_{17}O_4N$	61.9	6.5	5.9	62.14	6.82	5.6
II	6	96	229–230	70	$C_{19}H_{21}O_6N$	63.2	5.8	4.3	63.5	5.9	4.0
III	6	72	244–245	60	$C_{17}H_{17}O_4N$	67.9	5.6	4.5	68.21	5.73	4.7
IV	4	50	242	60	$C_{13}H_{17}O_4N$	62.3	6.9	5.8	62.14	6.82	5.6
V	4	100	234–236	65	$C_{19}H_{21}O_6N$	63.2	5.6	4.0	63.5	5.9	4.0

The condensation of 3,4-dihydroxy-β-phenethylamine (A) with α-keto-*n*-valeric acid in aqueous solution at *p*H 5-6 afforded 1-carboxy-6,7-dihydroxy-1-propyl-1,2,3,4-tetrahydroisoquinoline (I). Because of the lower solubility of 3,4-dimethoxyphenylpyruvic acid in water, the reaction with A was carried out in dioxane medium when the isoquinoline (II) was formed. In general, when the condensations were run in a dioxane medium, the isoquinoline derivatives separated from solution more rapidly and in purer form. Attempts to condense A with dimethylpyruvic acid, oxalacetic acid, and the sodium salt of oxalacetic ester under different conditions proved unsuccessful.

(1) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **VI**, p. 151 (1951).
(2) E. P. White, *New Zealand J. Sci. Tech.*, **25B**, 152 (1954); **33B**, 38 (1951).
(3) K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **75**, 5119 (1953).
(4) A. Chatterjee and N. A. Chaudhury, *Sci. and Culture*, **25**, 389 (1959).
(5) A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1909 (1959).