vating group. A related mechanism applies for the addition of diazomethane and diphenyldiazomethane to the double bond in maleic and fumaric esters[18] and maleic anhydride. The same addition product is obtained from the two esters and these when heated split off nitrogen to yield a *trans*-cyclopropane dicarboxylic acid. However, addition of diphenyldiazomethane to maleic anhydride yields a pyrazoline from which a *cis*-cyclopropane dicarboxylic acid is obtained. These results can be explained on the basis of an intermediate zwitterion addition product. In the case of the esters, as the C=C double bond is converted to a single bond in the intermediate, freedom of rotation is achieved resulting in identical pyrazolines, whereas in the case of the anhydride, no rotational freedom is achieved in the intermediate because of its cyclic nature. It has also been shown recently that the addition reactions of *p*-substituted diphenyldiazomethane to maleic ester and related compounds have rates consistent with the diazomethane acting as a nucleophile[19] and with there being an intermediate present in the reaction.

Acknolwedgment. We are grateful to the National Institutes of Health for financial support, and to Dr. Francis Smyth, Dr. Richard Baltzly and Mr. Ronald Brooks for helpful suggestions.

PROVIDENCE 12, R. I.

(18) *Cf.* J. van Alphen, *Rec. Trav. Chim.*, **62**, 210 (1943).

(19) N. B. Mehta, R. E. Brooks, and R. Baltzly, A.C.S. Meeting, Sept. 1960, New York City; paper #89, Abstracts of the Organic Chemistry Division.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

2-Phenylcyclobutylamine

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The DL-*cis* and -*trans* isomers of 2-phenylcyclobutylamine have been synthesized in a sequence of reactions involving DL-*cis*- and -*trans*-2-phenylcyclobutanecarboxylic acids and 2-phenylcyclobutanone. An improved route to 2-phenylcyclobutane-1,1-dicarboxylic acid is also reported.

The discovery[2] of the potent inhibition of monoamine oxidases[3] by 2-phenylcyclopropylamine[4] (tranylcypromine) made it of interest to compare the effect of ring-homologous phenylcycloalkylamines on such enzymes. 2-Phenylcyclopentylamine,[5] 2-phenylcyclohexylamine,[6] and 2-phenylcycloheptylamine[7] have been described in the literature and 3-phenylcyclobutylamine has recently been reported.[8] This article describes the synthesis of *cis*- and *trans*-2-phenylcyclobutylamines.

Since cyclobutanecarboxylic acids have been successfully degraded to amines,[9] 2-phenylcyclobutanecarboxylic acid appeared to be a suitable starting material for our purpose. An oily 2-phenylcyclobutanecarboxylic acid,characterized as the *p*-toluidide, has been synthesized by Burger and Hofstetter[10] by decarboxylation of 2-phenylcyclobutane-1,1-dicarboxylic acid. However, the yields both in the lengthy synthesis of this dicarboxylic acid and in the decarboxylation were so low that they severely limited that sequence for preparative purposes. A new and more rewarding synthesis of 2-phenylcyclobutane-1,1-dicarboxylic acid has therefore been developed.

Diethyl cinnamylmalonate (I) was prepared by the alkylation of diethyl malonate with cinnamyl chloride.[11] Addition of hydrogen bromide to this unsaturated ester gave diethyl (3-bromo-3-phenylpropyl)malonate (II) and this was cyclized to diethyl 2-phenylcyclobutane-1,1-dicarboxylate (III) with sodium hydride in tetrahydrofuran. Alkaline hydrolysis of III led to 2-phenylcyclobutane-1,1-dicarboxylic acid (IV) in a yield of 80% based on I. The compound was identical with that previously reported.[10]

$$C_6H_5CH{=}CHCH_2Cl \xrightarrow{Na^+\bar{C}H(CO_2C_2H_5)_2} C_6H_5CH{=}CHCH_2CH(CO_2C_2H_5)_2 \quad (I) \xrightarrow{HBr}$$

[1] Smith, Kline & French Laboratories Postdoctoral Fellow, 1959–61.

(2) R. E. Tedeschi, D. H. Tedeschi, P. L. Ames, L. Cook, P. A. Mattis, and E. J. Fellows, *Proc. Soc. Exptl. Biol. Med.*, **102**, 380 (1959).

(3) S. Sarkar, R. Banerjee, M. S. Ise, and E. A. Zeller, *Helv. Chim. Acta*, **43**, 439 (1960).

(4) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).

(5) See, for example, T. R. Govindachari, K. Nagarajan, B. R. Pai, and N. Arumugan, *J. Chem. Soc.*, 4280 (1956).

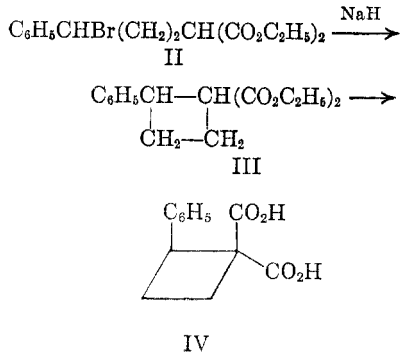
(6) See, for example, R. T. Arnold and P. N. Richardson, *J. Am. Chem. Soc.*, **76**, 3649 (1954).

(7) A. Burger, C. R. Walter, W. B. Bennett, and L. B. Turnbull, *Science*, **112**, 306 (1950).

(8) A. Burger and R. Bennett, *J. Med. and Pharm. Chem.*, **2**, 687 (1960).

(9) E. R. Buchmann, A. O. Reims, T. Skei, and M. J Schlatter, *J. Am. Chem. Soc.*, **64**, 2696 (1942).

(10) A. Burger and A. Hofstetter, *J. Org. Chem.*, **24**, 1290 (1959).

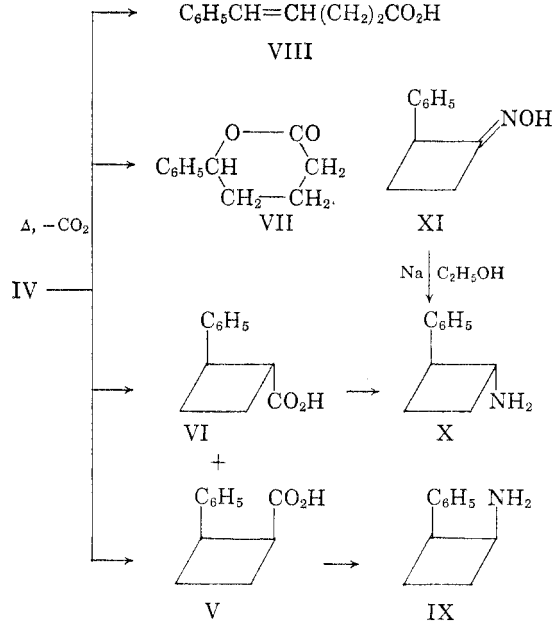


IV

Various conditions for the decarboxylation of the dicarboxylic acid (IV) have been examined. The most satisfactory methods proved to be those involving solvents, rather than the usual thermal decarboxylation of the molten malonic acid derivatives. Thus, chromatography of the mixture from a decarboxylation in refluxing mesitylene yielded two isomeric 2-phenylcyclobutanecarboxylic acids, the first a crystalline solid, and the second a liquid. Ozonization has been employed successfully in the configurational determination of 2-phenylcycloalkanecarboxylic acids, *e.g.* 2-phenylcyclopropanecarboxylic[12] and 2-phenylcyclohexanecarboxylic acids.[13] When applied to the crystalline 2-phenylcyclobutanecarboxylic acid, the major product was succinic acid, arising from fission of the 1-2 bond in the cyclobutane ring. However, there was also formed a small amount of *cis*-cyclobutane-1,2-dicarboxylic acid, demonstrating the *cis* configuration (V) of the solid acid. The isomeric oily acid is by inference the *trans* isomer (VI), and this assignment is supported by the results of reduction of 2-phenylcyclobutanone oxime (see below).

In addition to the stereoisomeric 2-phenylcyclobutanecarboxylic acids, a small amount (< 5%) of 5-phenyl-5-valerolactone (VII) was usually isolated from the decarboxylation mixture. A fourth component of this mixture was cinnamylacetic acid (VIII). This formed the bulk of the reaction product if the molten dicarboxylic acid (IV) was subjected to prolonged heating, and some polymer formation appeared to occur under these conditions. These components were practically absent if a solvent was used. That the cinnamylacetic acid did not arise through decomposition of the monocarboxylic acid (at least not the *cis* isomer), was shown by heating a sample of the acid (V) at 170–180° for one hour. The compound remained essentially unchanged under these conditions.

On the whole, the isolation of the pure (oily) *trans*-2-phenylcyclobutanecarboxylic acid proved quite laborious. As expected, the hindered *cis* acid is eluted first chromatographically and is easily purified by crystallization. In contrast, it is difficult to free the oily *trans* acid from traces of the *cis* isomer even by repeated chromatography. Although quantitative estimations are limited because of these difficulties, the *trans* acid appears to be the predominant isomer in the decarboxylation mixture, and this is confirmed by examination of the infrared spectrum of this mixture.[14]



Curtius degradation of the stereoisomeric 2-phenylcyclobutanecarboxylic acids V and VI yielded the corresponding 2-phenylcyclobutylamines IX and X in good yield. The intermediate azides were prepared advantageously from the acids by way of mixed ethyl carbonate anhydrides rather than from the acyl chlorides.[16] This method greatly improved preparative expediency although it was not needed to avoid the danger of isomerization of the *cis*- to the *trans*-series by way of the acid chlorides as is observed in the case of the 2-phenylcyclopropanecarboxylic acid.[4] In the cold at least, *cis*-2-phenylcyclobutanecarboxylic acid is not isomerized by thionyl chloride since the two

(11) D. Barnard and L. Bateman, *J. Chem. Soc.*, 926 (1950).

(12) G. W. Perold and H. L. DeWaal, *Chem. Ber.*, 85, 574 (1952).

(13) R. P. Linstead, S. R. Davis, and R. R. Whetstone, *J. Am. Chem. Soc.*, 64, 2009 (1942).

(14) M. Julia and A. Rouault[15] claimed to have cyclized ethyl 5-chloro-5-phenylvalerate to ethyl 2-phenylcyclobutanecarboxylate which on hydrolysis gave a crystalline acid of m.p. 90–91°. Through the courtesy of Prof. Julia we obtained a sample of this acid which we established to be cinnamylacetic acid by mixture melting point with an authentic sample, and comparison of the infrared spectra. In fact, prior to publication of the paper by Julia and Rouault we had attempted to cyclize ethyl 5-bromo-5-phenylvalerate with potassium isobutoxide but observed only ethyl cinnamylacetate as a reaction product.

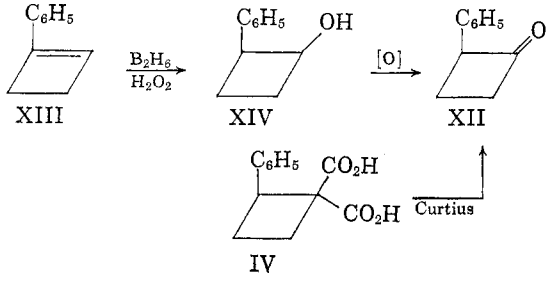
(15) M. Julia and A. Rouault, *Bull. soc. chim. France*, 1833 (1959); *Bull. soc. chim. France*, 979 (1960).

(16) We are obliged to Dr. Joseph Weinstock of Smith, Kline & French Laboratories for suggesting this modification. See J. Weinstock, *J. Org. Chem.*, in press.

acids, V and VI, give different *p*-toluidides *via* the acyl chlorides without extensive purification.

A second approach to 2-phenylcyclobutylamines started with 2-phenylcyclobutanone oxime (XI) which was reduced with sodium and ethanol to *trans*-2-phenylcyclobutylamine, identical with that obtained by Curtius degradation of the oily acid (VI). The reduction of ketones and oximes with metal combinations usually gives the thermodynamically more stable product,[17,18] and this is in accord with the formation of *trans*-2-phenylcyclobutylamine in this case.[19]

2-Phenylcyclobutanone (XII) was prepared by two routes. 1-Phenylcyclobutene[8] (XIII) was treated with diborane according to the general procedure of Brown[21] and the resulting adduct was oxidized and hydrolyzed to 2-phenylcyclobutanol (XIV), differing from 1-phenylcyclobutanol previously described.[8] A second, somewhat shorter and more convenient sequence, utilized the Curtius degradation[22] of 2-phenylcyclobutane-1,1-dicarboxylic acid.



EXPERIMENTAL

All melting points are corrected. Microanalyses by Mrs. Dolores Ellis.

Diethyl (3-bromo-3-phenylpropyl)malonate (I). Dry hydrogen bromide was passed through diethyl cinnamylmalonate[11] (276.3 g., 1.0 mole) over a period of 2 hr. The temperature rose to *ca.* 55° and was kept between 40 and 45° when the exothermic reaction ceased. The product was treated with ice water, and extracted with a mixture of benzene and ether. After washing the benzene solution with water and ice-cold 2% sodium bicarbonate solution, it was dried over sodium sulfate and the solvent removed at 90° (50 mm.). The product so obtained was used without further purification in the next step, as distillation caused decomposition.

2-Phenylcyclobutane-1,1-dicarboxylic acid (III). To a suspension of sodium hydride (48.0 g., 1.0 mole, 50% in oil) in tetrahydrofuran (1 l., distilled from lithium aluminum hydride) was added, slowly with stirring and cooling, under nitrogen, diethyl (3-bromo-3-phenylpropyl)malonate (1 mole) in tetrahydrofuran (100 ml.), at 0–5° over a period of 50 min. It is important that hydrogen starts to evolve early, otherwise the reaction becomes suddenly uncontrollable. The mixture was allowed to stand at 20° overnight and tetrahydrofuran was distilled off over a 75-min. period, until the internal temperature reached 80°. Ice was added and the mixture diluted with water. After separating the organic layer, the aqueous phase was extracted three times with ether and the combined organic layers were washed once with water. The solvent was removed and the residue saponified by treatment with refluxing potassium hydroxide solution (168 g., 3.0 moles in 500 ml. of 50% ethanol) over 3 hr. Most of the solvent was removed under vacuum on a water bath and the residue was taken up in water. The aqueous solution was washed twice with ether to remove the oil from the sodium hydride, and acidified with 37% hydrochloric acid (300 ml.). The organic acid which separated was isolated by ether extraction and crystallized from chloroform, yielding 2-phenylcyclobutane-1,1-dicarboxylic acid (173.7 g., 79% based on diethyl cinnamylmalonate), m.p. 173–174°, undepressed on admixture with a sample prepared by Burger and Hofstetter.[10] A further 11.4 g. of material, m.p. 169–172°, was collected from the mother liquor.

In a separate run, part of the crude diethyl 2-phenylcyclobutane-1,1-dicarboxylate was converted into the dihydrazide by refluxing with a solution of anhydrous hydrazine in butanol. The ether-washed product after crystallization from ethanol melted at 136–139°.

Anal. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.04; H, 6.49; N, 22.56. Found: C, 58.14; H, 6.61; N, 22.27.

Decarboxylation of 2-phenylcyclobutane-1,1-dicarboxylic acid. (a) 2-Phenylcyclobutane-1,1-dicarboxylic acid (40 g.) was heated in a retort at 10 mm. pressure and a bath temperature of 205–210°. Distillation set in and ceased after 15 min. The distillate (25.4 g.) was dissolved in a mixture of ether (30 ml.) and hexane (170 ml.), decanted from some insoluble oil, and chromatographed through a 53 × 145 mm. column of 100-mesh silica gel. Elution was carried out with a 15:85 mixture of ether-hexane, fractions of 100 ml. each being collected.

Fractions No. 4–12 consisted of a mixture of oil and crystals from which, by trituration with pentane, 5.5 g. of *cis*-2-phenylcyclobutanecarboxylic acid, m.p. 84.5–85°, was obtained. Rechromatographing the oily residue from these fractions on Fisher alumina (80–200 mesh) with an acetic acid–hexane mixture (2:98) yielded another 1.8 g. of the same material. For analysis, it was recrystallized from hexane. Characteristic infrared absorptions (in potassium bromide): 697, 730, 787 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.85; H, 6.60.

After some oily mixed materials, the last fractions eluted with the acetic acid-hexane mixture yielded 2.5 g. of an oily acid which, from its infrared spectrum (700, 753 cm.$^{-1}$ as a smeared film) was judged to be pure *trans*-2-phenylcyclobutanecarboxylic acid.

Fractions No. 17–22 yielded 90 mg. of a solid which, after crystallization from hexane, melted at 90.5–91° and proved to be cinnamylacetic acid by comparison of melting points, infrared spectra and mixture melting point with an authentic sample.[23] After the elution of cinnamylacetic acid, the concentration of ether in the eluant was increased to 50%. Some of the next fractions contained unchanged 2-phenylcyclo-

(17) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(18) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(19) Any possibility that the 2-phenylcyclobutyl group might have isomerized *inter alia* to 2-phenylcyclopropylmethyl[20] during the Curtius degradation of the acids V or VI was discounted by the properties of 2-phenylcyclopropylmethylamine (hydrochloride, m.p. 187–188°) (private communication, Dr. Charles L. Zirkle). The hydrochloride of *cis*-2-phenylcyclobutylamine melts at 224–226° (dec.), that of the *trans* isomer at 210–213° dec. (see Experimental). Likewise, hydrogenolysis of the cyclobutane ring of 2-phenylcyclobutanone oxime could be eliminated from consideration, since the material expected from such a reaction would be 4-phenylbutylamine, and its hydrochloride is known to melt at 164.5–165.5°.[8]

(20) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030, 5034 (1951).

(21) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).

(22) T. Curtius and G. Grandel, *J. prakt. Chem.*, **94**, 339 (1916).

(23) E. Erlenmeyer and A. Kreutz, *Ber.*, **38**, 3503 (1905).

butane-1,1-dicarboxylic acid, but fractions No. 31–42 yielded 5-phenyl-5-valerolactone[24] (1.75 g.) which crystallized from pentane as colorless needles, m.p. 73–75°, and was identified with an authentic sample by mixture melting point and comparison of the infrared spectra.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.82; H, 6.87.

(b) A solution of 2-phenylcyclobutane-1,1-dicarboxylic acid (40 g.) in mesitylene (150 ml.) was refluxed for 1.5 hr., cooled, and extracted with 70 ml. of ice-cold 15% sodium hydroxide solution. After being washed twice with ether, the alkaline solution was acidified at a temperature below 10°, the oil which separated was extracted with ether and chromatographed on silica gel as described under (a). Fractions No. 4–13 yielded *cis*-2-phenylcyclobutanecarboxylic acid (8.5 g.) on trituration with pentane. Rechromatography of the oily portion (13 g.) from fractions No. 4–7 on alumina using hexane-4% acetic acid gave another 1.2 g. of the *cis* isomer, and then 6.4 g. of pure *trans*-2-phenylcyclobutanecarboxylic acid.

(c) When 2-phenylcyclobutane-1,1-dicarboxylic acid was heated under reflux for 15 min. at 10 mm. pressure in a bath of 165–170°, or in 6*N* hydrochloric acid for 11 hr., and the reaction mixtures were worked up and chromatographed, cinnamylacetic acid was the only pure product which could be isolated.

Cis- and trans-2-Phenylcyclobutanecarboxy-p-toluidides. The respective acids (0.2 g.) were allowed to react with 1 ml. of thionyl chloride at 20° overnight, unchanged thionyl chloride was removed at 20° under reduced pressure, and the crude acyl chlorides were treated with a solution of 0.4 g. of *p*-toluidine in ether. The ether solutions were washed with dilute hydrochloric acid and water and evaporated.

The *cis*-*p*-toluidide crystallized from aqueous ethanol or from benzene-hexane as needles, m.p. 137–138°.

Anal. Calcd. for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.52.

The *trans*-*p*-toluidide crystallized from benzene-hexane, m.p. 162.5–164.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.36.

A mixture melting point with a sample of a 2-phenylcyclobutane-carboxy-*p*-toluidide previously described[10] gave no depression, and the infrared spectra of the two compounds were superimposable.

Cinnamylaceto-*p*-toluidide, prepared from cinnamylacetic acid in the same fashion, crystallized from benzene as plates, m.p.165.5-167°.

Anal. Calcd. for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.46.

A mixture melting point with *trans*-2-phenylcyclobutanecarboxy-*p*-toluidide was 135–142°.

Ozonization of cis-2-phenylcyclobutanecarboxylic acid. A solution of 1.23 g. of the *cis*-acid in 25 ml. of acetic acid was ozonized for 4 hr., then 30 ml. of 10% hydrogen peroxide was added, and the solution left at 25° overnight. It was evaporated almost to dryness on a water bath, the residue again treated with three 9-ml. portions of 10% hydrogen peroxide, and the solution evaporated. The gummy residue was divided into two portions. One portion was brought to crystallization on a porous plate; the solid was recrystallized from water, m.p. 189–189.5°, undepressed by admixture with succinic acid (m.p. 189–189.5°).

The other half was extracted thoroughly with hot benzene. The residue from the benzene extracts consisted of a mixture of oil and crystals. The latter were charcoaled in benzene solution, and furnished colorless material, m.p. 138.5–140.5°. A mixture melting point with authentic[9] *cis*-cyclobutane-1,2-dicarboxylic acid (m.p. 139.5–140.5°) was undepressed, and the infrared spectra of the two materials were identical.

(24) The 5-phenyl-5-valerolactone needed for comparison was prepared by reduction of 4-benzoylbutyric acid with sodium borohydride. It was vacuum distilled and crystallized from hexane as needles, or from ether-hexane as prisms, m.p. 75–76°. *Cf.* also M. Julia and A. Rouault.[15]

2-Phenylcyclobutanol. Diborane, generated[21] from boron trifluoride–ether complex (23.0 g., 0.16 mole) in Diglyme (48 ml.) by the addition of a solution of sodium borohydride (2.3 g., 0.06 mole) in Diglyme (60 ml.) was carried by a stream of nitrogen into a solution of 1-phenylcyclobutene[8] (15.4 g., 118 mmoles) in tetrahydrofuran (36 ml.) at 0–3° over a 1-hr. period. After another hour at 25°, ice was added cautiously keeping the temperature below 10°. This was followed by 3*N* sodium hydroxide solution (27 ml.) and then, after 20 min., by 15 ml. of 30% hydrogen peroxide below 10°. After another hour at 25° the mixture was diluted with water (90 ml.) and extracted three times with ether. The combined ether extracts were washed with water, dried over sodium sulfate, and fractionated. The fraction (14.4 g., 82%) boiling at 78–81°/0.27 mm., n_D^{25} 1.5480 was collected.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.63; H, 8.45.

The *phenylurethane* derivative melted at 118–120°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.09; H, 6.37; N, 5.59.

2-Phenylcyclobutanone. (a) A solution of 2-phenylcyclobutane-1,1-dicarboxylic acid (2.20 g., 0.01 mole) in acetone (4 ml.) and water (5 ml.) was treated at −5° to 0° with triethylamine (2.4 g., 24 mmoles) in acetone (20 ml.) followed by a solution of ethyl chloroformate (2.60 g., 24 mmoles) in acetone (5 ml.) as described above for *cis*-2-phenylcyclobutanecarboxylic acid. After conversion to the azide with sodium azide (1.96 g., 0.03 mole) in water (6 ml.) the mixture was stirred and worked up by ether extraction. The dried ether solution of the azide was then treated with 50 ml. of absolute ethanol. The ether was fractionated off, the ethanolic solution refluxed for 2 hr. and the solvent was removed. The residual orange oil was treated with 50 ml. of 2% sulfuric acid and steam-distilled, yielding 0.7 g. (48%) of colorless solid, b.p. 116°/7 mm., m.p. 27°.

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 81.77; H, 6.73.

The *semicarbazone* melted at 164–166°, and did not depress the melting point of the semicarbazone obtained by method (b).

(b) A solution of 2-phenylcyclobutanol (4.45 g., 0.03 mole), aluminum *t*-butoxide (4.9 g., 0.02 mole), and benzoquinone (16.2 g., 0.15 mole) in dry toluene (300 ml.) was stirred at 60–65° for 17 hr., then 1 ml. of water was added and the mixture filtered through a Celite pad. The filtrate was washed with three 100-ml. portions of 1*N* sodium hydroxide solution, then with water, the solvent was removed under reduced pressure and the residue extracted exhaustively with petroleum ether (b.p. 30–60°). This solvent was removed and the residual oil distilled, yielding 1.9 g. of colorless material, b.p. 65–68°/1–2 mm., $n_D^{22.5}$ 1.5464. This product did not analyze quite correctly but gave a solid sodium bisulfite adduct which was decomposed with 10% sodium carbonate solution. The ketone recovered from the adduct solidified when seeded with 2-phenylcyclobutanone obtained by method (a).

The *semicarbazone* melted at 163–165°.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.24; H, 6.54; N, 20.41.

The oxime was obtained by refluxing a solution of 2-phenylcyclobutanone (3.0 g., 0.02 mole), hydroxylamine hydrochloride (4.2 g.), and potassium hydroxide (2.2 g.) in 50% aqueous ethanol (30 ml.) for 15 hr., removing most of the solvent under reduced pressure and extracting the remaining suspension with ether. After washing, drying, and evaporating, the ether solution left 2.7 g. of a thick oil which did not crystallize. The infrared spectrum showed strong absorption at *ca.* 3300 cm.$^{-1}$ and medium absorption at *ca.* 1690 cm.$^{-1}$ It was reduced directly to *trans*-2-phenylcyclobutylamine as described below (method b).

cis-2-Phenylcyclobutylamine. To a stirred solution of *cis*-2-phenylcyclobutanecarboxylic acid (6.16 g., 35 mmoles) in acetone (15 ml.) and water (7.5 ml.) was added, at −5°, a solution of triethylamine (4.05 g., 5.55 ml., 40 mmoles) in

acetone (30 ml.) and then a solution of ethyl chloroformate (4.35 g., 3.85 ml., 40 mmoles) in acetone (10 ml.). After stirring the mixture at −5° to 0° for 30 min., a solution of sodium azide (3.25 g., 50 mmoles) in water (20 ml.) was added and stirring continued for another hour. The mixture was poured into 500 ml. of ice-cold saturated sodium chloride solution and 250 ml. of ice water, and extracted with five 75-ml. portions of ether. The combined ether extracts were dried over calcium sulfate, evaporated in a vacuum at 30°, and the residual azide was dissolved in 50 ml. of toluene. This solution was warmed slowly to 100° until nitrogen evolution ceased, the solvent removed under reduced pressure, and the residual isocyanate refluxed with 18% hydrochloric acid (35 ml.) for 12 hr. The cooled solution was made basic with 10% sodium hydroxide solution, the amine extracted with ether, the ether extracts were dried over sodium sulfate and evaporated. The oily amine (4.55 g.) boiled at 69°/0.8 mm., 68°/0.55 mm., n_D^{25} 1.5498. The yield was 4.15 g. (81%).

The *hydrochloride*, prepared in ether, crystallized from chloroform, m.p. 224–226° (sealed tube).

Anal. Calcd. for $C_{10}H_{13}N.HCl$: C, 65.37; H, 7.68; N, 7.63; Cl, 19.30. Found: C, 65.42; H, 7.71; N, 7.93; Cl, 19.07.

trans-2-Phenylcyclobutylamine. (a) This was prepared from *trans*-2-phenylcyclobutanecarboxylic acid as described for the *cis* isomer above. The yield was 63%, b.p. 72°/0.55 mm., n_D^{25} 1.5464. The *hydrochloride* was precipitated with ethereal hydrogen chloride and crystallized from ethanol-ether, m.p. 210–213° dec.

Anal. Calcd. for $C_{10}H_{13}N.HCl$: C, 65.37; H, 7.68; N, 7.63. Found: C, 65.09; H, 7.56; N, 7.75.

The *N-benzoyl derivative* was prepared by the Schotten-Baumann method and crystallized from ethanol, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{17}H_{17}NO$: N, 5.57. Found: N, 5.66.

(b) A solution of oily 2-phenylcyclobutanone oxime (1.6 g.) in absolute ethanol (70 ml.) was reduced by rapid addition of 6 g. of sodium. After the main reaction had ceased (15 min.), the mixture was refluxed for 35 min., the solvent removed under reduced pressure, the residue was treated with water (70 ml.) and the mixture extracted with ether. Basic material was extracted from the ether into 5% hydrochloric acid, the acid solution washed with ether, made alkaline with 40% sodium hydroxide solution, and the amine was extracted into ether. After drying over sodium sulfate and removal of the solvent, an oil remained, the infrared spectrum of which was identical with that of the amine obtained by method (a). The hydrochloride melted at 210–212° dec. and did not depress the melting point of the salt from method (a).

Attempts to reduce 2-phenylcyclobutanone oxime with lithium aluminum hydride or catalytically were unsuccessful.

CHARLOTTESVILLE, Va.

[CONTRIBUTION FROM UNION CARBIDE RESEARCH INSTITUTE AND THE LINDE CO. RESEARCH LABORATORY, UNION CARBIDE CORP.]

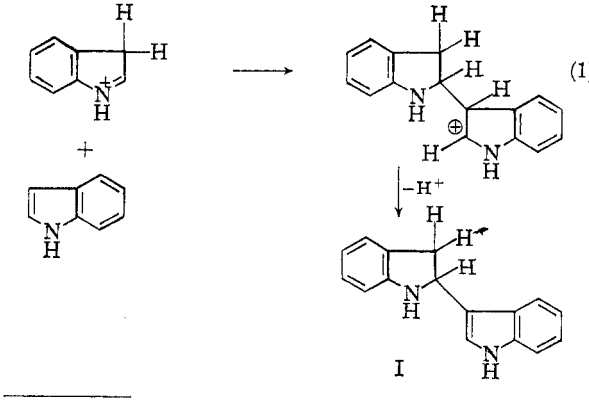
The Structure of Diskatole[1]

RICHARD L. HINMAN[2] AND E. R. SHULL[3]

Formula III has been established by NMR as the correct structure of diskatole. A crossed dimer of skatole and 2-methylindole has been prepared and its structure established as V.

It has been known for many years that indole forms crystalline dimers[4] and trimers[5] in acidic media, but it is only recently that the structures of these products have been established.[6] We became interested in the indole dimers, particularly in diskatole, in the course of studies on the relationship of the oxidation of indoles to their regulatory function in cellular growth.[7,8]

The structure of skatole dimer has not been established. The chemical evidence shows that it resembles diindole (I) in having an anilino nitrogen and an indole nitrogen, and in undergoing thermal depolymerization to the monomer.[9–11] The most recent structure proposed[11] for skatole dimer is shown in formula II. Since dimer formation involves the coupling of a protonated indole nucleus with an unprotonated one,[12] as shown for the formation of diindole (Equation 1), formation of structure II would require protonation of position-2



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