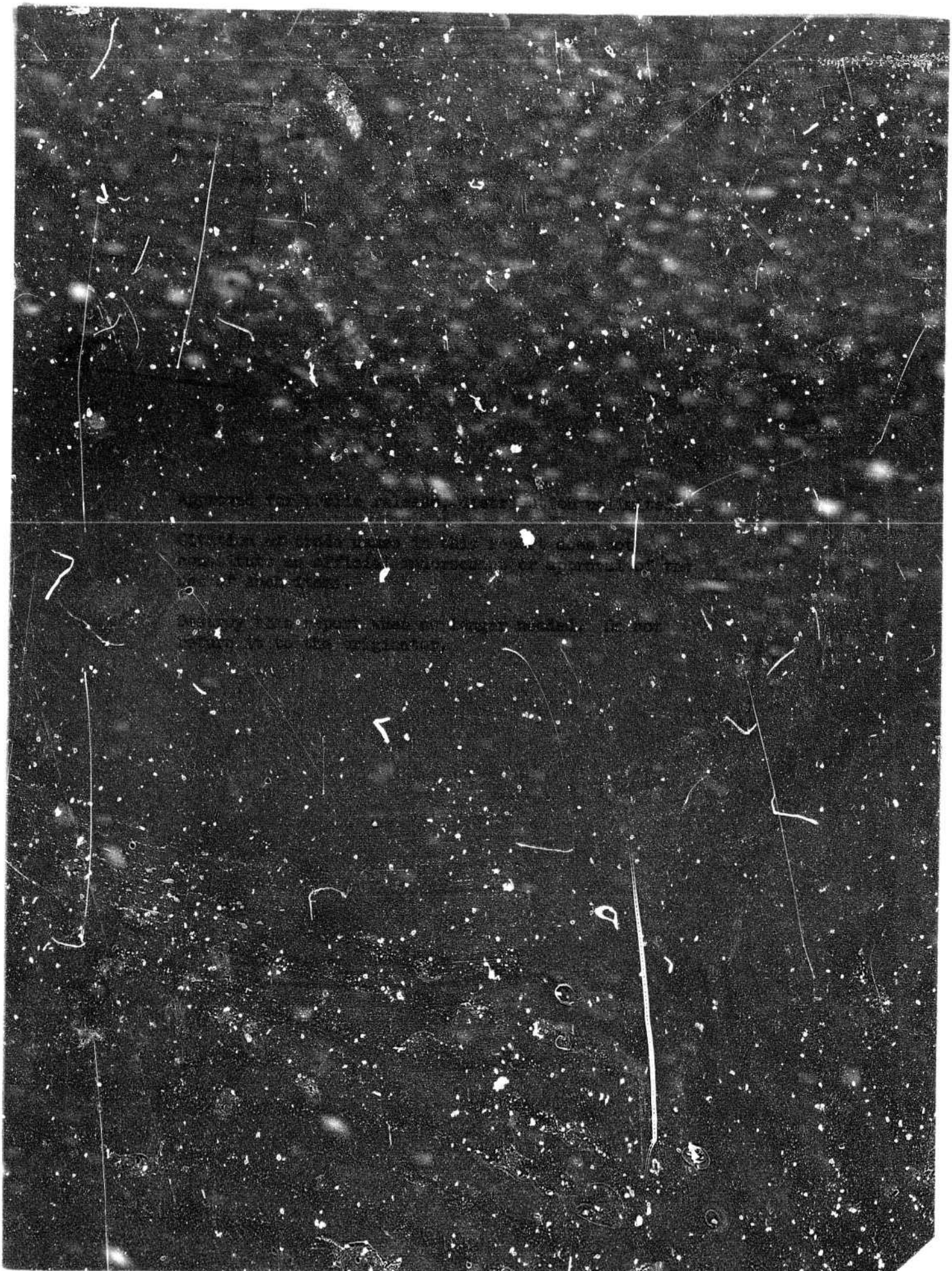

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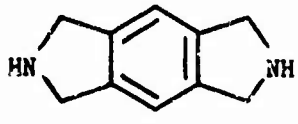
13. ABSTRACT

"Di-isoindoline", 1,2,3,5,6,7-hexahydrobenzo[1,2-c:4,5-c']dipyrrole (I) was recently synthesized and characterized by conversion to a number of derivatives. As a result, a new compound has been made available which is not only a potential



I

"Di-isoindoline"

monomer for the synthesis of new, thermally-stable copolymers but also a promising starting material for the synthesis of other new compounds which may prove useful in the field of medicine as antitussive, anticonvulsant, antitubercular and anthelmintic agents.

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TECHNICAL REPORT
72-17-CE

NOVEL SYNTHESIS OF "DI-ISOINDOLINE", A NEW HEXAHYDROBENZODIPYRROLE MONOMER

by

John T. Stapler
Joseph Bornstein

Project Reference
1T062105A329

SERIES: C&PLSEL - 90

November 1971

Clothing and Personal Life Support Equipment Laboratory
U. S. ARMY NATICK LABORATORIES
Natick, Massachusetts 01760

FOREWORD

This report was prepared by John T. Stapler under Task 02 A, Project 1T062105A329, Organic Materials Research for Army Materiel. The report covers work conducted primarily during the period 2 December 1968 to 1 June 1970 under the supervision of Dr. Joseph Bornstein. A portion of this research was submitted as a thesis in partial fulfillment of the requirements for the degree of Master of Science to the Department of Chemistry, Graduate School of Boston College, Boston, Massachusetts. The authors gratefully acknowledge contributions from personnel of the Pioneering Research Laboratory, U.S. Army Natick Laboratories: Dr. Ronald Chalk and Mr. Frank Bissett for data on nuclear magnetic resonance spectra and Mr. Maurice Bazinet for mass spectral data. Expressions of gratitude are extended to Dr. Richard Macnair of the Clothing and Personal Life Support Equipment Laboratory at Natick for his numerous reviews of this manuscript and his comments and suggestions.

NOVEL SYNTHESIS OF "DI-ISOINDOLINE",
A NEW HEXAHYDROBENZODIPYRROLE MONOMER

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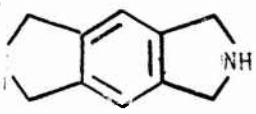
ABSTRACT

"Di-isoindoline", 1,2,3,5,6,7-hexahydrobenzo[1,2-c:4,5-c']-dipyrrole (I) was recently synthesized and characterized by conversion to a number of derivatives. As a result, a new compound has been made



I

"Di-isoindoline"

available which is not only a potential monomer for the synthesis of new, thermally-stable copolymers but also a promising starting material for the synthesis of other new compounds which may prove useful in the field of medicine as antitussive, anticonvulsant, antitubercular and anthelmintic agents.

I. Introduction

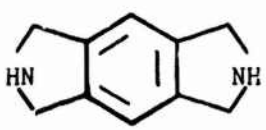
The military services have a continuous, pressing and acute need for materiel derived from high molecular weight, high-temperature polymers for use in clothing to protect personnel against the thermal effects of flame and radiation. While there are a number of high-temperature, organic polymers commercially available, only a few have been successfully converted to fibers, among which are aromatic polyamide homopolymers and copolymers, and polyimide and benzheterocyclic-imide copolymers containing benzimidazole, benzoxazole and benzthiazole units[1]. These stable, high-temperature and fiber-forming polymers are derived from monomers which possess characteristic chemical groups such as amide and imide linkages and some degree of conjugation. Much of their thermal stability is attributable to the number of aromatic rings[2] in the backbone of the polymer chain. Polyamides of this type are commonly prepared in one step by condensation of difunctional aromatic amine and acid chloride monomers. Imide and polybenzheterocyclic-imide polymers are obtained by a similar process which is followed by a second step involving self-condensation or ring closure with elimination of a coproduct[3].

II. Objective and Basis for Monomer Selection

The objective of this research was to synthesize one or more hexahydrobenzodipyrroles since these compounds are considered promising for synthesis of thermally stable benzheterocyclic polymers. A literature search revealed the possibility of seven different positional isomers of this structure. Although some of their derivatives are known, not one of these isomers has been isolated[7-19](See Table I).

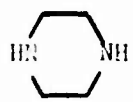
It was decided initially to attempt the preparation of 1,2,3,5,6,7-hexahydrobenzo[1,2-c:4,5-c']dipyrrole (I), which will be referred to in this communication as "di-isoindoline". Its selection as a potential monomer was based on the following:

1. The chemistry of I is expected to parallel that of piperazine which is already known to copolymerize to form thermally stable fibers and films[20,21]and impact-resistant nylon[22]. In addition, piperazine forms mono-and disubstituted derivatives which are useful as wool shrinkproofing agents[23], jet-fuel antistatic additives[24], anthelmintics[25,26], antispasmodics[27], antituberculars[28],



I

"Di-isoindoline"



Piperazine

TABLE I

HEXAHYDROBENZODIPYRROLES AND REFERENCES FOR THEIR DERIVATIVES

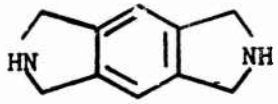
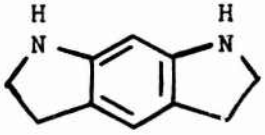
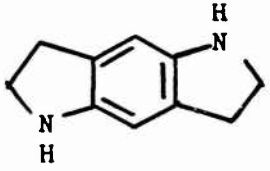
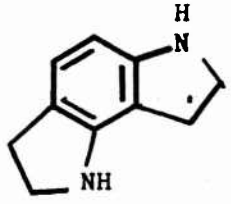
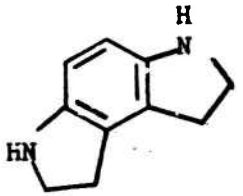
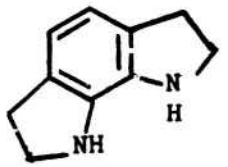
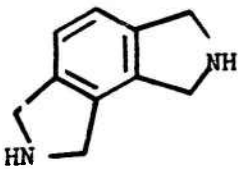
NO.	NOMENCLATURE	STRUCTURE
I.	1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']dipyrrole[4,5,6]	
II.	1,2,3,5,6,7-Hexahydrobenzo[1,2-b:5,4-b']dipyrrole[7,15]	
III.	1,2,3,5,6,7-Hexahydrobenzo[1,2-b:4,5-b']dipyrrole[7,16]	
IV.	1,2,3,6,7,8-Hexahydrobenzo[1,2-b:3,4-b']dipyrrole[13,17,18]	

TABLE I (CONTINUED)

HEXAHYDROBENZODIPYRROLES AND REFERENCES FOR THEIR DERIVATIVES

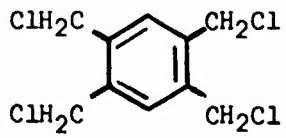
NO.	NOMENCLATURE	STRUCTURE
V.	1,2,3,6,7,8-Hexahydrobenzo[1,2-b:4,3-b']dipyrrole (16)	
VI.	1,2,3,6,7,8-Hexahydrobenzo[2,1-b:3,4-b']dipyrrole (16)	
VII.	1,2,3,6,7,8-Hexahydrobenzo[1,2-c:3,4-c']dipyrrole (19)	

anticonvulsants[29] and cockroach insecticides[30]. It has been found that one piperazine derivative improves the dye receptivity of nylon[31]. Thus on the basis of this analogy, "di-isoindoline" copolymers and derivatives would be expected to have similar useful characteristics.

2. The presence of the aromatic ring in the diamine monomer would allow the synthesis of fully and semi-aromatic systems necessary for copolymers which provide good thermal protection.

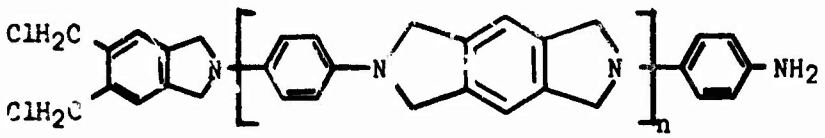
III. History

In 1947 Ruggli and Geiger[4] described their attempts to prepare I. They condensed 1,2,4,5-tetrakis(chloromethyl)benzene (VIII) with various aromatic and aliphatic diamines and reported the isolation of I as its dihydrochloride salt. However, in spite of considerable effort, they were unable to isolate I as the free base and concluded that this molecule could not be prepared by the rational method of adding alkali to the corresponding dihydrochloride salt. Eleven years later, Ried and Grabosch[5], utilizing the same methods, prepared



VIII

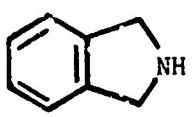
three new derivatives of "di-isoindoline". Then, in 1965, Shono et al.[7] condensed seven aromatic diamines with VIII and thereby directly obtained "di-isoindoline" copolymers in minute quantities. It is noteworthy that one of these, poly(N,N'-diphenylene-dipyrrolino-benzene) (IX), underwent thermal decomposition between 400 and 500°C. No thermal data was given for Shono's six other copolymers.



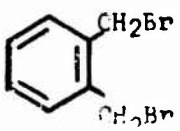
IX

IV. Synthetic Route

The synthesis of "di-isoindoline" undertaken in the study reported herein followed modification of established procedures for preparing 1,3-dihydroisoindole (X) from o-xylylenedibromide (XI)



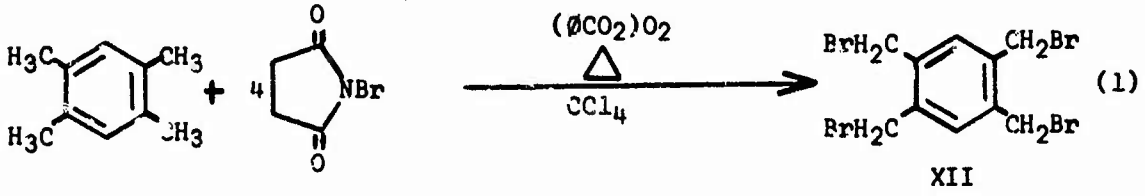
X



XI

and p-toluenesulfonamide. The reaction sequence is shown below (reactions 1-4). Reactions 5-11 were carried out in order to characterize and verify the structure of I and also to prepare a monosubstituted product which would serve as an intermediate in an attempt to prepare an isoindole derivative (XX) at a later date.

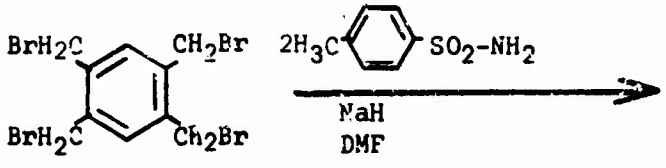
Synthesis of 1,2,4,5-Tetrakis(bromomethyl)benzene (VII)



(1)

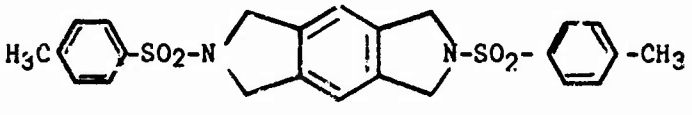
XII

Synthesis of 1,2,3,5,6,7-Hexahydro-2,6-di(p-tolylsulfonyl)benzo[1,2-c:4,5-c']dipyrrole (XIII)



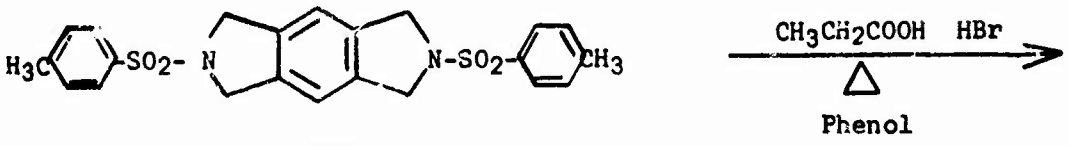
XII

(2)

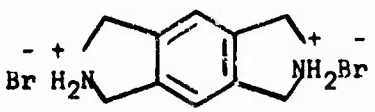


XIII

Synthesis of 1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']-dipyrrole Dihydrobromide (XIV)

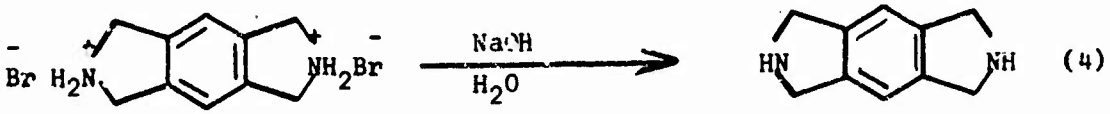


XIII (3)



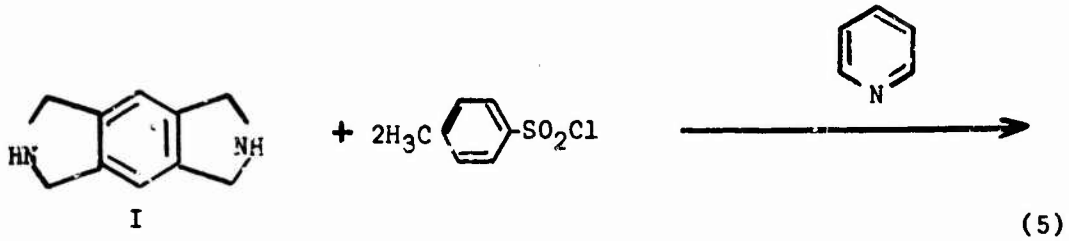
XIV

Synthesis of 1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']-dipyrrole (I) ("Di-isoindoline")

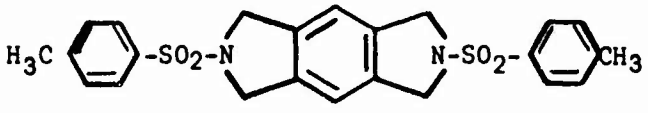


XIV I (4)

Ditosylation of 1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']-dipyrrole (I) to form 1,2,3,5,6,7-Hexahydro-2,6-di-(p-tolylsulfonyl)benzo[1,2-c:4,5-c']dipyrrole (XIII)

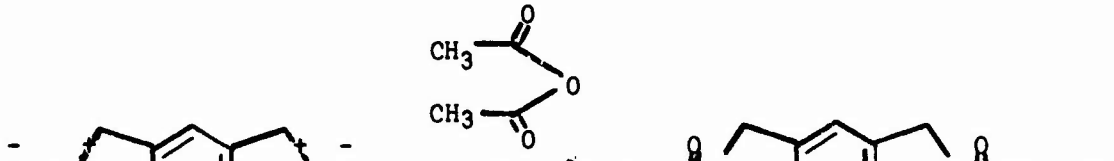


I (5)



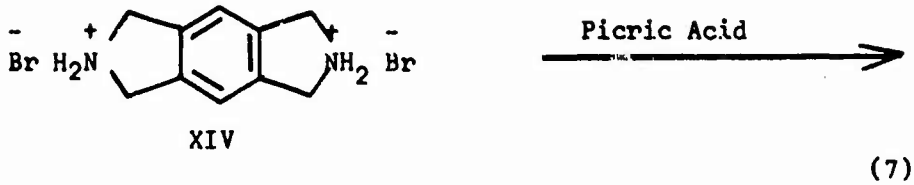
XIII

Diacetylation. Synthesis of 1,2,3,5,6,7-Hexahydro-2,6-diacetylbenzo[1,2-c:4,5-c']dipyrrole (XV)



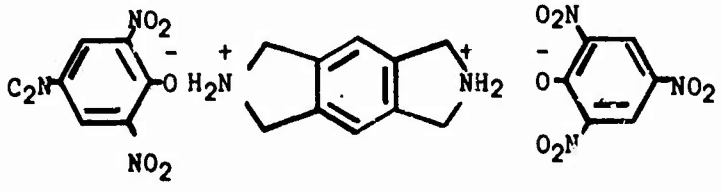
XIV XV (6)

Synthesis of 1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']-dipyrrole Dipicrate (XVI)

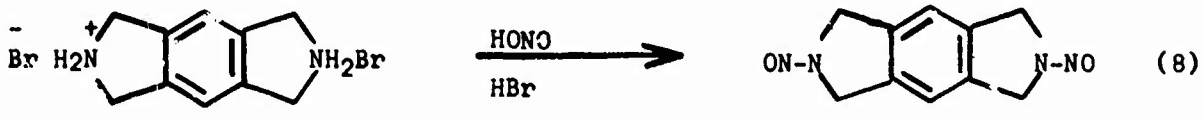


XIV

(7)

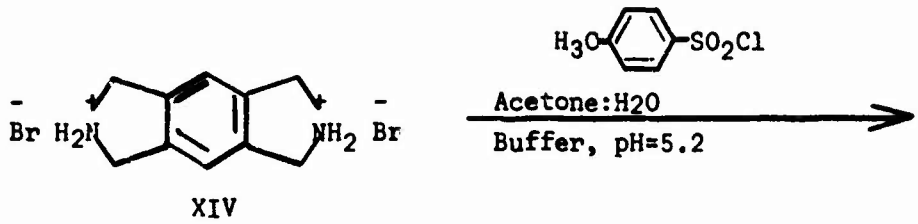


Di-nitrosation. Synthesis of 1,2,3,5,6,7-Hexahydro-2,6-dinitrosobenzo[1,2-c:4,5-c']dipyrrole (XVII)

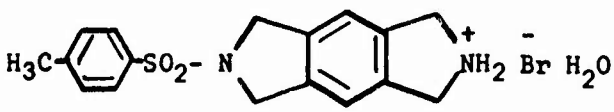


XIV XVII (8)

Synthesis of 1,2,3,5,6,7-Hexahydro-2-(p-tolylsulfonyl)benzo[1,2-c:4,5-c']dipyrrole Monohydrobromide Monohydrate (XVIII)



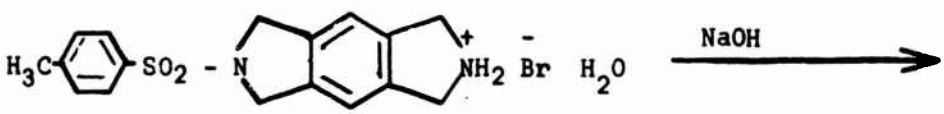
XIV



(9)

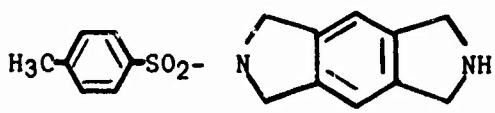
XVIII

Synthesis of 1,2,3,5,6,7-Hexahydro-2-(p-tolylsulfonyl)benzo[1,2-c:4,5-c']dipyrrole (XIX)



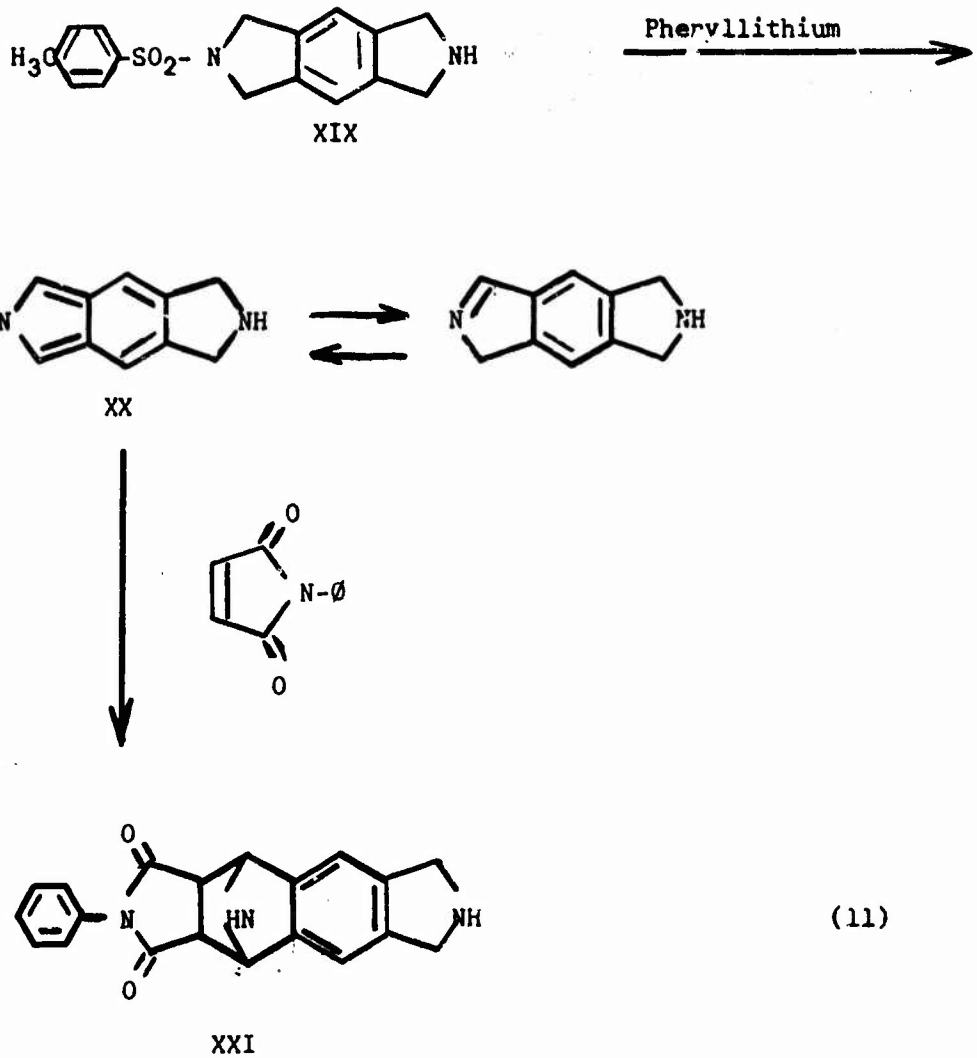
XVIII

(10)



XIX

Attempted Synthesis of an Isoindole, 2,5,6,7-Tetrahydrobenzo[1,2-c:4,5-c']dipyrrole (XX) and Diels-Alder Adduct (XXI)


Phenyllithium
XIX
XX
XXI
(11)

V. Results

"Di-isoindoline", 1,2,3,5,6,7-hexahydrobenzo[1,2-c:4,5-c']dipyrrole (I) was successfully prepared and isolated for the first time by use of the above synthetic route; identification was established by chemical and spectral means. Compound I, when dry, was found to be relatively stable in air; over a mixture of Ascarite and Drierite in a nitrogen atmosphere I is stable indefinitely at room temperature. The diamine dihydrobromide salt may be stored indefinitely without any special precautions.

In the course of characterizing this new compound, the following four derivatives were prepared:

1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']dipyrrole Dihydrobromide (XIV)

1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']dipyrrole Dipicrate (XVI)

1,2,3,5,6,7-Hexahydro-2-(p-tolylsulfonyl)benzo-[1,2-c:4,5-c']dipyrrole Monohydrobromide Monohydrate (XVIII)

1,2,3,5,6,7-Hexahydro-2-(p-tolylsulfonyl)benzo-[1,2-c:4,5-c']dipyrrole (XIX)

"Di-isoindoline" has thus been successfully monosubstituted and this makes it possible to synthesize 2,6-unsymmetrically disubstituted "di-isoindolines" analogous to certain known physiologically active piperazine derivatives.

Results of the attempted synthesis of the isoindole (XX)

and Diels-Alder adduct (XXI) were inconclusive. While XX could not be isolated, its presence in solution was confirmed by tests (see paragraph VI A 11 below). The suspected derivative, XXI, was isolated in poor yield.

VI. Discussion of Results

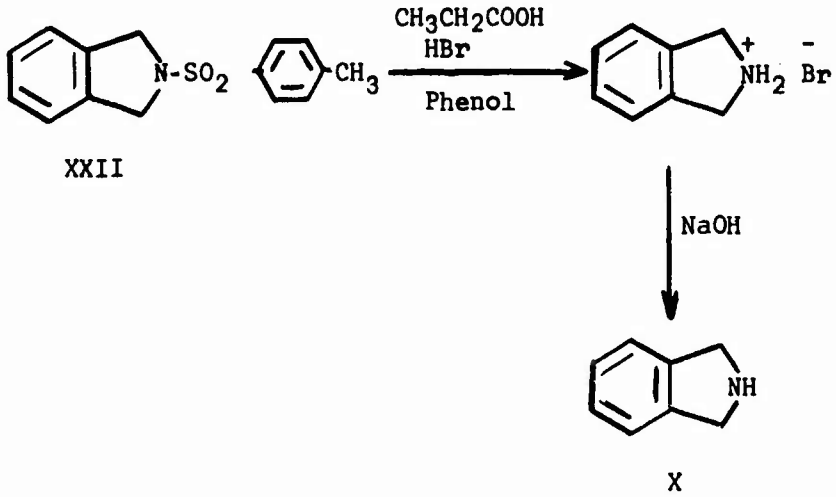
A. Synthetic Route

1. The procedure of Rind and Bodem[32] was initially used to prepare 1,2,4,5-tetrakis(bromomethyl)benzene (XII), but it was impossible to obtain the reported yield of pure product (25%). Ultimately an alternative procedure was found which increased the yield to 35-40%. In this method a mixture of durene and N-bromosuccinimide was heated and irradiated simultaneously with a 300-watt photoflood lamp to effect reaction.

2. Bornstein and Shields[33] had earlier prepared 2-(p-tolylsulfonyl)dihydroisoindole by the reaction of o-xylylene dibromide (XI) and p-toluenesulfonamide. Following this procedure, XI was converted to 1,2,3,5,6,7-hexahydro-2,6-(p-tolylsulfonyl)benzo [1,2-c:4,5-c']dipyrrole (XIII).

3. The next step involved cleavage of the ditosyl groups of XIII in order to liberate the diamine monomer (I) as its dihydrobromide salt (XIV). Cleavage of compound (XIII) had been carried out previously by hydrolysis with concentrated sulfuric acid followed by reaction with acetyl chloride to form the diacetyl derivative (XV)[4,34]

This process required caution because certain sulfonamides are known to undergo rearrangement and sulfonation in the presence of concentrated sulfuric acid[35]. More recently, sulfonamides have been effectively cleaved by sodium-naphthalene[36] as well by solution of HBr in acetic acid-phenol[37]. The method followed was that used by Bornstein and Shields[38] for the preparation of 1,3-dihydroisoindole (X). As shown below, they cleaved the tosyl derivative (XXII) with a hydrobromic acid-propionic acid-phenol mixture. Phenol acted as a bromine acceptor and thus protected the aromatic amine. In this reaction

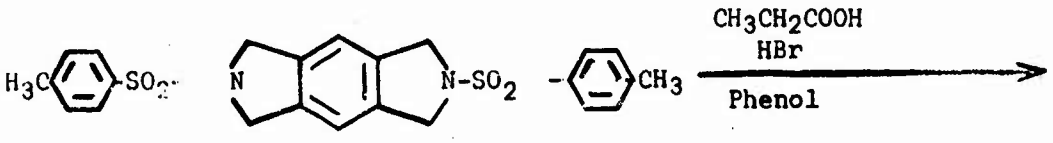


XXII

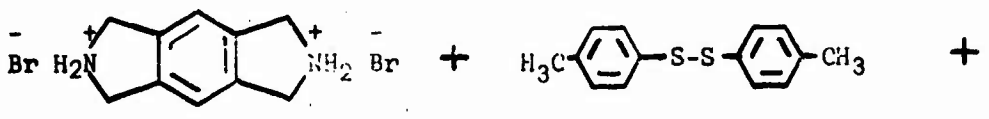
X

reduction afforded the disulfide (XXIII) while the bromine was oxidized. Although intermediates were not isolated, the reaction involving XIII is believed to proceed as shown below, since the anticipated product XIV and the major byproduct XXIII were obtained. Occasionally formation of some tar occurred toward the end of the reflux period. The dihydrobromide (XIV) was fortunately easily removed from the reaction

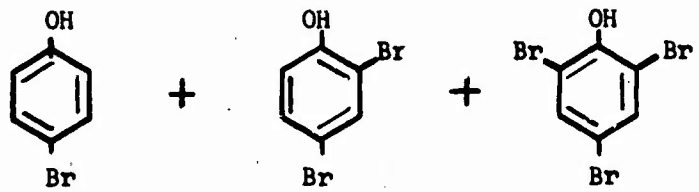
mixture by repeated extractions with hot water. Cleavage of the tosyl groups was also accomplished by using hydrobromic acid in combination with m-cresol as both solvent and bromine acceptor. Both



XIII



XIV XXIII



of the foregoing cleavage methods afforded nearly identical yields of product.

4. "Di-isoindoline" (I) was liberated by reaction of the dihydrobromide salt with base. The white crystals, when dried, gradually darkened over a period of 9-24 hours; indefinite storage was possible over a 1:1 mixture of Drierite and Ascarite in a

nitrogen atmosphere. The nmr and ir spectra corresponded favorably to the assigned structure I. The molecular weight as determined by mass spectroscopy and neutralization equivalent was found to be in agreement with theory.

5. When treated with p-toluenesulfonyl chloride in pyridine at room temperature, "di-isoindoline" (I) gave the expected ditosyl derivative (XIII).

6. The diacetyl derivative of "di-isoindoline" was prepared by treating the dihydrobromide salt with acetic anhydride according to the procedure of Shriner, Fuson and Curtin[39].

7. The reaction of the "di-isoindoline" dihydrobromide salt with picric acid following the procedure of Vogel[40] gave dipicrate (XVI).

8. Secondary amines, upon treatment with nitrous acid, are known to yield nitrosamines[41]. As expected the N,N'-dinitroso derivative (XVIII) of "di-isoindoline" was readily prepared and isolated as a faint, yellow crystalline solid by treatment with nitrous acid.

9. The p-tosyl monohydrobromide monohydrate (XVIII) of "di-isoindoline" was isolated and identified as an intermediate during synthesis of the monotosyl derivative (XIX). The procedure followed was similar to that used for monotosylating piperazine[42] with p-toluenesulfonyl chloride under carefully controlled conditions. At a predetermined pH value of 5.2, XVIII was obtained. As expected, some N,N'-di-p-tosyl "di-isoindoline" (XIII) was formed during the

reaction since at this pH (the equivalence point) tosylation of either or both nitrogen atoms of the molecule can occur on a statistical basis. A small amount of the starting material was also recovered.

10. The monotosyl derivative (XIX) of "di-isoindoline" was obtained in near quantitative yield by treating XVIII with base. It is less sensitive to air oxidation than "di-isoindoline".

11. Some indications of success were obtained from attempts to prepare and isolate the isoindole species (XX) following the procedure of Shields and Bornstein[43] utilizing sodium-naphthalene. Negative results had been obtained from earlier attempts to cleave the tosyl group of XIX with either freshly prepared phenyllithium or potassium t-butoxide. After XIX had been allowed to react with sodium-naphthalene, pine splint and Ehrlich's[44] tests of the ethereal extracts were positive, indicating the presence of the isoindole moiety. Evaporation of a portion of the solution produced a green substance which darkened rapidly in air. Reaction of the remaining solution with N-phenylmaleimide afforded a material believed to be a Diels-Alder adduct on the basis of infrared examination (see experimental section). Diels-Alder adducts of isoindoles to one known dissociate upon heating to reform the initial isoindole[44]. Positive Ehrlich's and pine splint tests of a solution of our heated adduct proved that a pyrrole-type ring had indeed been formed. Efforts to isolate XX were not pursued further since the principal object of the investigation, the preparation and characterization of "di-isoindoline", had been attained.

B. Comparisons with the work of Ruggli and Geiger

Ruggli and Geiger[4] reported the preparation of a number of "di-isoindoline" derivatives, three of which we have synthesized, namely, the ditosyl (XIII), diacetyl (XV) and dinitroso (XVII) compounds. Some inconsistencies in the properties of our products with those reported were noted and compared.

a. Melting points

Melting points of the ditosyl, diacetyl and dinitroso derivatives of "di-isoindoline" were not clearly defined. At high temperatures they tended to decompose without melting, proceeding from white or faint yellow to blackness. The decomposition ranges, therefore, were determined by recording the temperatures of (1) the incipient color change of the compound and (2) the formation of tar or char. A comparison of results obtained is given on Table II.

b. Elemental analyses

Elemental analyses are compared on Table III where the results reported by Ruggli and Geiger on compounds XIII and XV are shown to differ considerably from the calculated values.

TABLE II

COMPARISON OF MELTING POINTS OF

"DI-ISOINDOLINE" DERIVATIVES

"DI-ISOINDOLINE" COMPOUND	NLABS (°C)	RUGGLI AND GEIGER (°C)
Ditosyl (XIII)	246-248 (dec)	300-360 (dec)
Diacetyl (XV)	252-314 (dec)	300 (dec)*
Dinitroso (XVII)	222-225 (dec)	260 (dec)

* The diacetyl derivative of Ruggli and Geiger was reported to contain one to two moles of water.

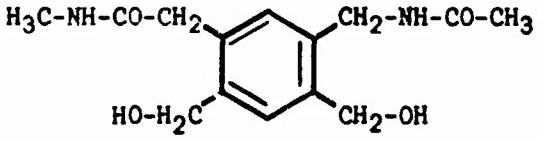
TABLE III

COMPARISON OF ELEMENTAL ANALYSES OF "DI-ISOINDOLINE" DERIVATIVES

"DI-ISOINDOLINE" DERIVATIVE	ELEMENT	CALCULATED	FOUND	RUGGLI AND GEIGER
Ditosyl (XIII)	C	61.51	61.74	60.28
	H	5.16	5.67	5.21
	N	5.98	6.04	5.53
	S	13.69	13.24	Not given
Diacetyl (XV)	C	67.87	68.11	61.36
	H	6.81	6.58	7.36
		11.82	11.45	10.77
Dinitroso (XVII)	C	55.04	54.94	55.15
	H	4.62	4.89	4.74
	N	25.68	25.41	25.77

c. Hydrated diacetyl derivative

Ruggli and Geiger believed their diacetyl compound (XV) to be hydrated with one to two moles of water and they consequently proposed the ring-opened structure XXIII.



XXII

In contrast, the diacetyl compound we prepared was not hydrated. Later, following the identical method of Ruggli and Geiger, we prepared a specimen of XV which, when analyzed, likewise proved to be free of water and was identical in all respects with our original sample prepared by acetylation of I.

d. Isolation of the free base (I)

Ruggli and Geiger were unable to obtain "di-isoindoline" as the free base from a solution of the dihydrochloride by the usual method of adding a suitable base. Upon evaporating the solvent from their reaction mixture, they recovered a brown, powdery residue which was extremely sensitive to carbon dioxide and which successfully resisted all attempts to effect purification. Consequently, to prove the dihydrochloride salt structure, other methods were employed and further efforts to purify the residue were abandoned. Our initial, successful synthesis of "di-isoindoline" was accomplished by alkaline treatment of its dihydrobromide salt. Later we prepared a sample of

Ruggli and Geiger's dihydrochloride salt of "di-isoindoline" and also treated it with base. The resulting product was, as expected, the free base, "di-isoindoline".

VII. Experimental

A. Instruments - see Appendix

B. Materials - see Appendix

C. Procedures

1. Synthesis of 1,2,4,5-Tetrakis(bromomethyl)benzene(XII)

A 500-ml three-necked flask containing 275 ml of carbon tetrachloride was fitted with a large condenser, mechanical stirrer, thermometer and heating mantle. Added to the flask in the following order were these recrystallized reagents: 16.8 g (0.125 mol) durene; 89.1 g (0.50 mol) N-bromosuccinimide (NBS); and 3 g (0.0124 mol) benzoyl peroxide. While stirring vigorously to keep the insoluble NBS in suspension, the mixture was slowly heated to reflux temperature. At this point excessive foaming occurred which necessitated temporary removal of the heat source. Frothing diminished after about 2 min. and reflux action continued uninterrupted for about 30 min. Succinimide, an insoluble co-product, was removed by filtration while the solution was still hot. Cooling the filtrate over night in the refrigerator afforded 17 g of a white, semi-waxy solid, mp 114-140.5°C. One recrystallization from cold chloroform gave 8.55 g (14.8%) of XII as colorless granules; mp 157-159°C. (lit. [32] 160°C). The latter

product was sufficiently pure for the next synthetic step. For analytical purposes, a second recrystallization was effected from acetonitrile; recovery of the product approximated 50%.

Anal. Calcd. for $C_{10}H_{10}Br_4$: C, 26.70; H, 2.24; Br, 71.06. Found: C, 26.63; H, 2.27; Br, 71.18.

The second procedure did not require the benzoyl peroxide catalyst. In this method the same apparatus and technique were employed except for the heating mantle which was replaced by a 300-watt photoflood lamp which served both as a source of heat and source of photochemical activation. The yield of XII was 35-40% under these conditions.

2. Synthesis of 1,2,3,5,6,7-Hexahydro-2,6-di-(p-tolylsulfonyl)benzo[1,2-c:4,5-c']dipyrrole (XIII)

A 1-l, three-necked flask was fitted with an efficient stirrer (preferably a mechanical type), thermometer and a pressure-equalizing dropping funnel that carried an inlet for admission of dry nitrogen. The entire assembled apparatus was dried by heating with a soft flame (or electric heat gun) as a brisk stream of nitrogen was passed through the system. The flow of nitrogen was reduced to about 5 ml per minute. Into the cooled flask was placed 12.98 g (0.300 mol) of 56% sodium hydride dispersed in mineral oil and 90 ml of purified dimethylformamide (DMF). The mixture was stirred at room temperature and a solution of 25.9 g (0.150 mol) of p-toluenesulfonamide (freshly recrystallized) in 90 ml of purified DMF was added dropwise over a period of 75 min.

Slow addition was necessitated by excessive foaming. The walls of the flask were then quickly washed down with 30 ml of DMF while the condenser was momentarily removed. The resulting suspension was stirred at room temperature for 1 hr and at 65°C for an additional hr (a water bath). Then a solution of 33.9 g (0.075 mol) of 1,2,4,5-tetrakis(bromomethyl)benzene(XII) in 300 ml of purified DMF was added dropwise with vigorous stirring at such a rate as to maintain a temperature of 65-70°C. Subsequently the dark brown reaction mixture was stirred at room temperature for 3 hr and poured into 600 ml of ice water in a 2-l Erlenmeyer flask. After standing overnight the creamy brown precipitate was collected by suction filtration, washed three times with 200-ml portions of hot acetone followed by three additional washings with 100-ml portions of hot water. Twenty grams (56.6%) of the crude, light-yellow precipitate (mp 150-240°C. with slow decomposition during the entire range) was collected, air-dried and dissolved in 350 ml of m-cresol at a temperature of 138-148°C. (Decomposition occurred at temperatures above this range). After cooling to room temperature, an equal volume of methanol was added and a fine, faint-yellow crystalline XIII precipitated. The solid was collected, washed with cold methanol, and dried over phosphorus pentoxide in a vacuum desiccator. The yield of XIII was 1.9 g (53%); mp 246.5-248°C (dec) (lit[4] no melting up to 360°C; darkens above 300°C); sodium fusion: positive for sulfur, nitrogen, negative for halogen; ir (KBr) 1155 and 1335 (C-SO_2-N); nmr [$(F_3C)_2CHOH$] δ 2.42 (s,6,CH_3), 2.96 (s,8CH_2), 7.00 (s,2,ϕ), 7.38-7.78 (m,8,ϕ).

Anal. Calcd. for $C_{24}H_{24}N_2O_4S_2$: C, 61.51; H, 5.16; N, 5.98; O, 13.66; S, 13.69. Found: C, 61.74; H, 5.67; N, 6.04; O, 13.31; S, 13.24.

3. Synthesis of 1,2,3,5,6,7-Hexahydrobenzo-[1,2-c:4,5-c']dipyrrole Dihydrobromide (XIV)

In a 1-l round-bottomed flask were placed 39.6 g (0.085 mol) of XIII, 50.28 g (0.53 mol) phenol, 616 ml (5.45 mol) of redistilled 48% hydrobromic acid and 263.9 ml of propionic acid. The flask was fitted with a reflux condenser and connected to a source of low-pressure nitrogen, an oil bubbler, a safety trap and a powerful magnetic stirrer. The mixture was heated to reflux, and after 5 min a brief period of foaming ensued. Reflux was continued for 52 hr. During this period the color of the mixture changed from red to deep brown. Cooling over night at room temperature produced a cream-colored precipitate which was collected on a Buchner funnel and air dried. The solid was taken up in 250 ml of boiling water and a hot-water insoluble material was removed by filtration, which, when recrystallized from m-cresol was found to be 1.12 g (2.8%) of unreacted XIII. Also separated was about 0.2 g char. The aqueous filtrate containing XIV was treated with 100 ml of 48% HBr and then placed in the refrigerator for 12 hr. Long, transparent crystals were collected and recrystallized once from 38% HBr containing charcoal. A second recrystallization gave 24.43 g (90%) of the dihydrobromide XIV, mp 268-270°C (dec); Sodium fusion: positive for halogen and nitrogen, negative for sulfur; ir 2800 (NH_2).

Anal. Calcd. for $C_{10}H_{14}Br_2N_2$: C, 37.30; H, 4.38; Br, 49.63; N, 8.69. Found: C, 37.33; H, 4.50; Br, 49.40; N, 8.61.

(Note: During some subsequent cleavage reactions, the mixture blackened during the reflux period and a water-insoluble tar or char was present in the residue after chilling. Nevertheless the dihydrobromide of "di-isoindoline" was removed by successive water extractions, decolorizing and reprecipitation with an excess of hydrobromic acid. The yield of product was unchanged).

The foregoing procedure was modified by substituting m-cresol for phenol, in which case only about 20% of the cleaving agents (hydrobromic and propionic acids) was necessary. In this case 8.42 g (0.018 mol) of XIII, 104 ml m-cresol, 24 ml of 48% HBr and 24 ml propionic acid were used. After a reflux period of 17.5 hrs, the crude yield was 4.65 g (82%); the main product was isolated and purified by the procedure described above.

4. Synthesis of 1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']-dipyrrole (I) ("Di-isoindoline")

Five grams (0.01 mol) of the dihydrobromide XIV was dissolved in a minimum amount of hot water (about 20 ml). While stirring the solution vigorously a large excess (3.2 ml) of 33% NaOH was added. A white solid separated immediately. The suspension was quickly chilled in an ice-cold bath, the solid collected by filtration and washed three times with 10-ml portions of ice-cold water. After partial drying for 10-15 min under a stream of dry nitrogen, the solid was transferred with a minimum exposure to the atmosphere

to a desiccator and dried under vacuum over phosphorus pentoxide for 24 hrs. The yield of "di-isoindoline" (I) was 1.53 g (96.5%), mp 166-167°C (dec). A small sample was sublimed (111°C/2 mm) for analysis; ir (KBr) 3330 (NH), 408 (C-N-C); nmr ($CDCl_3$) δ 2.15 (s,2,NH), 4.18 (s,8,CH_2), 7.07 (s,2,ϕ); mass spectrum (70 ev) m/e (rel intensity) 160 (92, M^+),, 159 (97, M-1) 142 (8), 132 (68), 131 (83), 130 (100), 117 (78), 103 (69), 102 (45), 91 (20), 78 (58), 77 (86), 63 (80), 52 (62), 50 (81), 41 (35), 39 (82), 28 (96).

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.90; H, 7.64; N, 17.07.

A sample of I weighing 0.0741 g (463 mmol) was titrated with 0.0482N hydrochloric acid and the titration monitored with a pH meter. A plot of pH versus milliliters of acid showed an inflection in the curve between 16 and 22 ml. The equivalence point was determined graphically to occur at a pH value of 5.2. [This value was used to prepare the monotosyl derivative (XIX) of "di-isoindoline"]. Milliliters of 0.0482N HCl: Calcd. for two -OH equivalents, 19.24. Found, 19.2.

The molecular weight of I was determined from the foregoing titration by calculating the neutralization equivalent (factor) as follows:

$$\text{Neutralization equivalent} = \frac{\text{weight of sample} \times 100}{\text{vol of acid (ml)} \times \text{NF}}$$

$$= \frac{0.07431 \times 1000}{19.2 \times 0.0482}$$

$$= 80.13$$

Mol. wt.: Calcd for $C_{10}H_{12}N_2$ = 160.22. Found: 80.13 x 2 = 160.26.

"Di-isoindoline" was found to decompose in a desiccator when stored over phosphorus pentoxide in a nitrogen atmosphere. Stability for an indefinite period was found possible when the product was stored over a 1:1 mixture of Drierite and Ascarite in a nitrogen atmosphere at room temperature.

5. Conversion of 1,2,3,5,6,7-Hexahydrobenzo-[1,2-c:4,5-c']dipyrrole (I) to 1,2,3,5,6,7-Hexahydro-2,6-di(p-tolyl-sulfonyl)benzo[1,2-c:4,5-c']dipyrrole (XIII)

One gram (6.24 mmol) of "di-isoindoline" (I) was dissolved in 100 ml of pyridine in a 250-ml flat-bottomed flask. With stirring, 2.3 g (12.48 mmol) of p-toluenesulfonyl chloride was added dropwise at room temperature. The yellow precipitate which formed immediately was collected after 1 hr., washed with acetone, recrystallized from m-cresol/methanol and dried by suction. The pale yellow, fine crystalline material (2.9 g, 97%); mp 246-248°C (dec), was identified as XIII by its infrared spectrum and melting point.

6. Synthesis of 1,2,3,5,6,7-Hexahydro-2,6-diacetyl-benzo[1,2-c:4,5-c']dipyrrole (XV)

A sample of the dihydrobromide (XIV) (3.2 g, 0.01 mol) was dissolved in about 20 ml cold water in a 100-ml flat-bottomed flask. At room temperature, 1.91 ml (0.02 mol) acetic anhydride was added dropwise to the stirring mixture. A white precipitate slowly formed. After an hour it was removed by filtration and sucked dry. Recrystallization from a 1:1 methanol-ethanol solution

afforded 2.5 g (92%) of XV as fine, white crystals: mp 252-314°C (dec.) (lit[4]. 300°C dec.); ir (KBr) 1610(CO).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 67.87; H, 6.81; N, 11.82; O, 13.50. Found: C, 68.11; H, 6.58; N, 11.45; O, 13.86.

7. Synthesis of 1,2,3,5,6,7-Hexahydrobenzo-[1,2-c:4,5-c']dipyrrole Dipicrate (XVI)

The dihydrobromide (XIV) (3.2 g, 0.01 mol) was dissolved in 10 ml cold water and 10 ml of a saturated solution of picric acid in ethanol was added. The mixture was stirred at room temperature and allowed to stand overnight. The needle-like yellow crystals were collected, washed twice with 5 ml cold ethanol and dried by suction. Recrystallization from ethanol gave 5.1 g (82%) of the dipicrate (XVI); mp 220-240°C (dec.).

Anal. Calcd. for $C_{22}H_{18}N_8O_{14}$: C, 42.73; H, 2.93; N, 18.12; O, 36.22. Found: C, 43.16; H, 3.26; N, 17.70; O, 35.88.

8. Synthesis of 1,2,3,5,6,7-Hexahydro-2,6-dinitroso-benzo[1,2-c:4,5-c']dipyrrole (XVII)

The dihydrobromide (XIV) (3.3 g, 0.01 mol) was added to 100 ml water containing 12 drops of 48% hydrobromic acid. To the stirring solution at room temperature was added a solution of 1.4 g (0.02 mol) sodium nitrite in 7 ml water over a period of about 10 minutes. A magma of fine crystals formed soon after the initial addition. The mixture was allowed to stand at room temperature overnight and the precipitated product was filtered. The crude XVII was recrystallized from 150 ml of 50% ethanol.

Refrigeration overnight yielded 1.72 g (78.8%) after drying over phosphorus pentoxide; mp 222-225°C (lit[4]. 260°C dec.); ir (KBr) 1445 (N-NO).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68; O, 14.66. Found: C, 54.94; H, 4.89; N, 25.41; O, 14.76.

9. Synthesis of 1,2,3,5,6,7-Hexahydro-2-(p-tolylsulfonyl)benzo[1,2-c:4,5-c']dipyrrole Monohydrobromide Monohydrate (XVIII)

The dihydrobromide (XIV) (11.22 g, 0.05 mol) together with 412 ml of a 2:1 acetone-water mixture and 262 ml sodium acetate-acetic acid buffer solution (pH = 4.58) were placed in a 1-liter beaker equipped with a magnetic stirrer. The mixture was moderately stirred until all or almost all of the salt had dissolved. The electrodes of a previously calibrated and standardized pH meter were immersed in the solution; the initial pH reading was 5.43. A solution of 48% hydrobromic acid was added dropwise and slowly until a reading of 5.2 was observed. By this time all residual salt particles had dissolved. A dropping funnel containing 6.7 g (0.035 mol) p-toluenesulfonyl chloride in 113 ml acetone was set up over the beaker and the contents added dropwise over a period of 70 min. A pH value of 5.2 was strictly maintained during this period by the addition of a drop or two of 33% sodium hydroxide solution as required. Five minutes after initiation of the addition, a milk-white precipitate appeared and became heavier as the addition proceeded. After completion of the addition of tosyl chloride, a pH value of 5.2 was maintained for an additional hr.

The mixture was transferred to a 2-l flat-bottomed flask and the acetone was boiled off. Hardened filter paper was used to collect the white solid. One recrystallization from m-cresol-methanol followed by drying gave 4.75 g (58%) of the ditosyl derivative (XII). Evaporation of the filtrate to one half its volume and refrigeration overnight afforded 4.27 g (41.8%) of XVIII in platelets; mp 240-248°C (dec.). (Unreacted starting material was recovered in trace amounts by adding concentrated hydrobromic acid to the mother liquor and refrigerating). An analytical sample was prepared by recrystallizing XVIII from 95% ethanol. Sodium fusion: positive for sulfur, nitrogen and halogen; ir (KBr) 1160-1155 (C-SO_2-N), 2930 (NH_2).

Anal. Calcd. for $C_{17}H_{21}BrO_3SN_2$: C, 49.40; H, 5.12; Br, 19.33; O, 11.61 S, 7.76; N, 6.78. Found: C, 49.67; H, 4.95; Br, 19.64; O, 11.57; S, 7.52; N, 6.72.

10. Synthesis of 1,2,3,5,6,7-Hexahydro-2-(p-tolyl-sulfonyl)benzo[1,2-c:4,5-c']dipyrrole (XIX)

The monohydrobromide monohydrate (XVIII) (0.659 g, 1.6 mmol) was warmed (not boiled) with 30-40 ml water in a 100 ml flat-bottomed flask until all particles had dissolved. An excess (about 1.5 ml) of 33% sodium hydroxide solution was added to the hot solution and a white fluffy precipitate formed immediately. After chilling, the material was filtered, washed twice with cold water and dried over a 1:1 mixture of Drierite and Ascarate over nitrogen in a vacuum desiccator. XIX was obtained as a white crystalline product, 0.49 g (97%); mp 185°C (dec.); ir (KBr) 3375 (NH), 1155 and 1330

(C-SO_2-N); nmr ($CDCl_3$) δ 2.15 (s,1,NH), 2.39 (s,3,CH_3), 4.15 (s,4,CH_2), 4.56 (s,4,CH_2). 7.00 (s,2,ø), 7.26-7.74 (m,4,ø).

Anal. Calcd. for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91; O, 10.18; S, 10.20. Found: C, 64.48; H, 5.88; N, 8.94; O, 10.73; S, 10.07.

11. Attempted Syntheses of an Isoindole, 2,5,6,7-Tetrahydrobenzo[1,2-c:4,5-c']dipyrrole (XX) and Diels-Alder Adduct (XXI)

A dry 250-ml flask was fitted with a magnetic stirrer, condenser and T-tube for maintaining a dry nitrogen atmosphere. To a solution of 6.41 g (0.05 mol) of naphthalene in 70 ml of dried 1,2-dimethoxyethane was added 1.15 g (0.05 gram-atom) of sodium. The reaction mixture was stirred for 2 hours under dry nitrogen to give a dark green solution approximately 0.70M in sodium-naphthalene. Then 3.08 g (0.0095 mol) of XIX was quickly added in one portion and stirring was continued at room temperature for 75 min under nitrogen. After chilling, cold water (about 60 ml) added until all particles had just dissolved and the water layer was barely discernible. The mixture was extracted with five 100-ml portions of ether; the yellow extracts were then combined and dried over magnesium sulfate for 1 hr. Pine splint and Ehrlich's tests of the solution were strongly positive indicating the presence of a pyrrole ring. A portion of the solution was evaporated to dryness to produce a green residue which darkened rapidly on exposure to the atmosphere. The remaining ethereal solution was concentrated to a volume of 20 ml and a solution of 0.5 g (3,2 mmol) of N-phenyl-maleimide in 32 ml of ether was added. After standing four days, about 3 mg of a white crystalline substance had precipitated. After recrystallization from methanol and drying, the infrared spectrum

(KBr pellet) showed a very strong carbonyl band at 1710 cm^{-1} and N-H band at 3430 cm^{-1}. This would be normally expected of such an adduct. Tests for the pyrrole ring were negative. There was not a sufficient amount of material for either n.m.r or elemental analysis. A small specimen of the solid was heated to its decomposition point in a test tube. Addition of water and ethanol to this material gave a solution which reacted positively in the usual tests for the pyrrole ring. This observation suggests that an adduct was actually formed, because such adducts are known to revert to their progenitors on thermolysis[43].

VIII. Conclusions

1,2,3,5,6,7-Hexahydrobenzo[1,2-c:4,5-c']dipyrrole, also called "di-isoindoline", has been synthesized and characterized both spectroscopically and by means of suitable derivatives. It is a potential starting material for numerous syntheses and is suitable for copolymerization to form new copolymers. Evidence of the potential of "di-isoindoline" as a monomer for producing high thermal capacity polysulfones and polyamides is obtained from the observed high melting points of the ditosyl (XIII) and diacetyl (XV) derivatives.

IX. Future Work

An initial program is currently in motion to synthesize and characterize a series of "di-isoindoline" copolymers under Project No. 1T061101A91A.

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APPENDIX

ADDITIONAL EXPERIMENTAL DETAILS

A. Instruments

1. Nuclear magnetic resonance spectra: Models A-60 and HA100, Varian Associates. Tetramethylsilane was used as the internal standard.

2. Mass spectra: Model 110B, High Resolution Mass Spectrophotometer, Consolidated Electrodynamics.

3. Infrared spectra: Perkin-Elmer 521 Grating Spectrometer.

4. Melting points: Thomas-Hoover "Unimelt".

5. pH: Corning Model 12 pH Meter.

B. Materials - All reagents were ACS grade or better. Chemicals requiring additional purification are listed below.

1. Durene (1,2,4,5-tetramethylbenzene): recrystallized from ethanol; mp 191-193°C.

2. Benzoyl peroxide: Recrystallized from chloroform and methanol; mp 103°C.

3. N-Bromosuccinimide: Recrystallized from water and dried over phosphorus pentoxide; mp 172-174°C.

4. N,N-Dimethylformamide: dried over 13X Linde molecular sieves and distilled under reduced pressure; bp 76°C.

5. p-Toluenesulfonamide: recrystallized from water and dried over phosphorus pentoxide under vacuum; mp 134-135°C.

6. N-Phenylmaleimide: recrystallized from cyclohexane and dried; mp 85.5-87°C.

7. Carbon tetrachloride: shaken consecutively with KOH, sulfuric acid, water; separated and dried over calcium chloride and, finally, distilled at atmospheric pressure; bp 76.8°C.

8. Sodium nitrate: recrystallized from water and dried over phosphorus pentoxide.

9. 48% Hydrobromic acid: redistilled and the 126°C fraction collected.

10. p-Toluenesulfonyl chloride: recrystallized from a 1:20 mixture of benzene and 60-80°C petroleum ether; mp 69-71°C.