



THE SYNTHESIS AND REACTIONS OF SOME
BIHETEROCYCLIC SYSTEMS

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BIHETEROCYCLIC SYSTEMS

By

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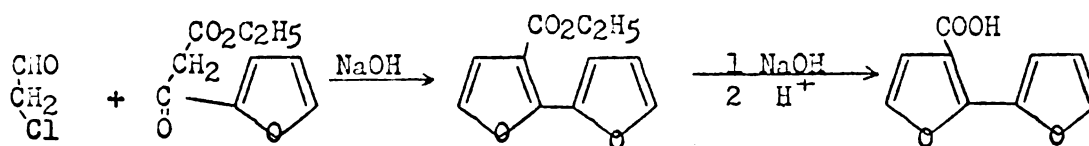
INTRODUCTION AND HISTORICAL

In recent years, considerable work has been undertaken in these laboratories on the syntheses and investigation of biheterocyclic compounds. One objective of this research was to utilize these compounds in determining the orienting effects of the hetero-aromatics furan, pyrrole, and thiophene as substituents in substitution reactions. Some progress has been made in these studies in that the biheterocyclic systems 2-(2'-thienyl)-furan and 3-(2'-thienyl)-furan have been synthesized in sufficient quantities to permit orientation studies (1). However, the yields have been small due to the necessity of employing a multistep reaction sequence in their preparation. It would be very helpful to the investigation of the properties and chemistry of biheterocyclic compounds to develop a synthetic method to such systems capable of yielding substantial amounts of symmetrical and mixed biheterocyclics.

In the present research, investigations of two possible reaction sequences to the synthesis of biheterocyclics were examined. The first of these dealt with an examination of a coupling reaction reported by Gronowitz (2), utilizing an oxidation reduction coupling procedure involving the lithium derivative of the heterocyclic molecule and anhydrous cupric chloride.

Gronowitz employed this method to synthesize 2,2'-bithienyl and 3,3'-bithienyl in yields substantially higher than any preparation previously described in the literature (3). The present investigation extended this coupling procedure to the synthesis of the furan and N-methylpyrrole biheterocyclic systems.

The preparation of 2,2'-bifuryl was initially accomplished in 1926 by Kondo and Suzuki (4) through the decarboxylation of 2,2'-bifuryl-3-carboxylic acid. The acid was obtained in approximately a twenty percent yield by a two step synthesis involving furoylacetate and 2-chloroethanal as starting materials.



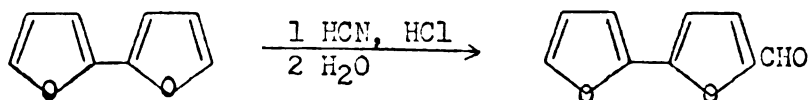
Since that time, little work has been reported in the literature on the 2,2'-bifuryl system, especially with respect to the development of a simple synthesis of this material.

A thorough search of the chemical literature shows that the synthesis of 2,2'-bi-N-methylpyrrole has not been as yet accomplished; or at least it has not been reported.

In the present research, investigations were carried out to synthesize derivatives of the biheterocyclic systems 2,2'-bifuryl and 2,2'-N-methylpyrrole. The intermediate utilized to synthesize all derivatives was the metalated biheterocyclic lithium compound.

The use of this intermediate lead directly to the carboxylic acid, carboxaldehyde, and methyl ketone of the two biheterocyclic compounds described above, with all of the substituent groups located in the 5 position.

The 5-carboxylic acid and 5-carboxaldehyde of 2,2'-bifuryl were initially prepared by Reichstein, Grussner, and Zschokke in 1932 (5). These investigators synthesized the aldehyde via the action of hydrogen cyanide and dry hydrogen chloride on 2,2'-bifuryl. The aldehyde was then oxidized to the carboxylic acid.



The second reaction pathway to the preparation of biheterocyclic systems investigated involved the coupling of the lithium derivative of a heterocyclic molecule with the same or another heterocyclic halide. This procedure had been investigated recently by Ramanathan and Levine (6). These investigators reacted 2-thienyllithium with a series of alkyl bromides and a haloaromatic compound, bromobenzene. The alkyl halides coupled with the thienyllithium giving excellent yields of the alkyl thiophenes. The reaction of 2-thienyllithium with bromobenzene gave a thirty percent yield of 2-phenylthiophene, and a small amount of 2,5-diphenylthiophene. Ramanathan and Levine (7) extended their

coupling reactions to furan, but limited their studies here to reactions with alkyl halides.

The coupling reactions investigated in the present work were conducted in tetrahydrofuran as well as in ether as reaction solvents. The tetrahydrofuran was the better of the two solvents with regard to product yield in the reactions investigated by Ramanathan and Levine. No 2-phenylthiophene was produced when ether was employed as the reaction solvent.

With the successful arylation of thiophene with the fairly unreactive bromobenzene, it seemed reasonable that the synthesis of biheterocyclics utilizing heterocyclic halides, specifically halothiophenes, could be successful and should be investigated.

EXPERIMENTAL¹

2-Furyllithium, C_4H_3LiO : M.W. 73.99

The method of Ramanathan and Levine (?) was utilized in the preparation of 2-furyllithium. A 20.4 g. quantity of furan (0.30 mole) was added to 0.25 moles of n-butyllithium in 400 ml. of anhydrous ether during a half hour period. The reaction was carried out in a nitrogen atmosphere by a continuous passage of nitrogen through the one liter three-necked reaction vessel at -20° . After the addition of the furan, the reaction mixture was allowed to warm to room temperature, and was then heated at its reflux temperature an additional four hours to complete the reaction.

The yield of the organoheterocyclic, 76%, was based upon the amount of 2-furoic acid produced by addition of the 2-furyllithium to an ether slurry of carbon dioxide.

2,2'-Bifuryl, $C_8H_6O_2$: M.W. 134.10

A solution of 2-furyllithium was prepared as previously described by the addition of 20.4 g. (0.30 mole) of furan to 0.25 moles of n-butyllithium in ether. The total volume of the reaction mixture was increased to a half liter by the addition of 100 ml. ether following the formation of the 2-furyllithium. The reaction

¹ All melting and boiling points are uncorrected.

mixture was cooled to -10° , and 33.6 g. (0.25 mole) of anhydrous cupric chloride was added to the 2-furyllithium ether solution from a dropping funnel during a half hour period. Initially the reaction mixture turned a dark green from a pale green in a matter of a few minutes, after which it was stirred rapidly at 0° for three and a half hours and then poured into 300 ml. of a saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted twice with 250 ml. of ether, and the combined ether layers were dried over anhydrous calcium sulfate. The ether was removed by distillation, and the liquid residue was vacuum distilled to obtain 7.06 g. (0.052 mole, 42%) of pure product as a colorless liquid; b.p. $62-63^{\circ}/11$ mm. Literature (5) value, b.p. $63-64^{\circ}/11$ mm.

2-Lithium-N-methylpyrrole, C_5H_6LiN : M.W. 87.03

The method of Shirley (8) was modified to obtain this compound. N-methylpyrrole, 32.4 g. (0.40 mole), in 50 ml. anhydrous ether was added during a period of a half hour to a solution containing 0.37 moles n-butyllithium in 600 ml. of anhydrous ether. The reaction was conducted in a one liter three-necked flask under a nitrogen atmosphere at a reaction temperature of -25° . Following the addition of the heterocyclic ether solution, the reaction mixture was allowed to warm to room temperature, and heated at its reflux temperature for twelve hours. The work of Shirley indicates a maximum yield of 42% based on the amount of 2-N-methylpyrrole carboxylic acid produced by carbonation of the

lithium derivative with an ether slurry of solid carbon dioxide.

2,2'-Bi-N-methylpyrrole, $C_{10}H_{12}N_2$: M.W. 160.37

An ether solution of 2-lithium-N-methylpyrrole was prepared as described above by adding 32.4 g. (0.40 mole) N-methylpyrrole to 0.37 moles n-butyllithium. After heating the reaction mixture at its reflux temperature for twelve hours, it was cooled to -10° , and 50.4 g. (0.37 mole) cupric chloride was added to it during a half hour period. The reaction solution turned a dark grey from a pale yellow on addition of the cupric chloride. The reaction was allowed to continue for an additional three hours at 0° . The reaction mixture was then poured into 400 ml. of saturated aqueous ammonium chloride. The water layer was extracted twice with 200 ml. ether, and the combined ether extracts were dried over anhydrous calcium sulfate. The ether was removed by evaporation and the residue, a dark blue oil, was distilled under reduced pressure to obtain 12.1 g. (0.075 mole, 42%) of the desired product; b.p. $86^{\circ}/1$ mm.

Anal: Calculated for $C_{10}H_{12}N_2$: C, 75.00; H, 7.50; N, 17.50

Found:¹ C, 74.73; H, 7.70; N, 16.71

2,2'-Bi-N-methylpyrrole,5-carboxaldehyde, $C_{11}H_{12}N_2O$: M.W. 188.37

2,2'-Bi-N-methylpyrrole, 12.1 g. (0.075 mole) in 40 ml. of

¹ Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

ether, was added during a period of 15 minutes to 0.08 moles n-butyllithium at -25° . The reaction was conducted in a 500 ml. three-necked flask under a nitrogen atmosphere with vigorous stirring. Following the addition of the heterocyclic, the reaction mixture was allowed to warm to room temperature, and heated at its reflux temperature for seven hours. The ether solution of the lithium derivative of the bi-N-methylpyrrole was cooled to -40° , and 5.84 g. (0.08 mole) N,N-dimethylformamide in 30 ml. ether was added to it slowly. A white fluffy solid separated from solution immediately. The suspension was stirred for a half hour during which it warmed to room temperature, and then it was poured into 200 ml. of a saturated aqueous ammonium chloride solution. The water layer was extracted twice with 50 ml. ether, and the combined ether extracts were dried over anhydrous calcium sulfate. The ether was removed by evaporation, and the residue was vacuum distilled to obtain 4.1 g. (0.022 mole, 32%) of a yellow oily product boiling at $113^{\circ}/0.07$ mm. The oil crystallized on being set aside at room temperature. Recrystallization of the crude product from ligroin gave a colorless crystalline product. It melted at $50-50.5^{\circ}$, and had a sharp carbonyl peak at 5.98μ in the infrared.

Anal: Calculated for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.33; N, 14.89

Found: C, 70.03; H, 6.49; N, 14.74

2,2'-Bi-N-methylpyrrole, 5-methyl ketone, $C_{12}H_{14}N_2O$: M.W. 202.38

An 11.5 g. (0.072 mole) quantity of 2,2'-bi-N-methylpyrrole

in 30 ml. ether was added to 0.086 moles n-butyllithium in ether. The apparatus and experimental reaction conditions employed here were those described for the preparation of 2,2'-bi-N-methylpyrrole,5-aldehyde. The quantities of reactants used were 7.0 g. (0.072 mole) of N,N-dimethylacetamide in 40 ml. ether added to the lithium heterocyclic solution at -25° . A white solid precipitated immediately; however the reaction was allowed to continue for two hours during which the reaction mixture heated to room temperature. Product isolation was carried out as previously described in the preparation of the aldehyde. Distillation of the crude product yielded 3.7 g. (0.018 mole, 26%) of a light yellow oil boiling at $110^{\circ}/0.07$ mm. The oil crystalized upon being set aside at room temperature; m.p. $44-44.5^{\circ}$. Recrystallization of the crude product from ligroin gave a colorless crystalline material with a sharp carbonyl peak at 6.01μ in the infrared.

Anal: Calculated for $C_{12}H_{14}N_2O$: C, 71.28; H, 6.93; N, 13.86

Found: C, 71.12; H, 7.17; N, 13.59

2,2'-Bi-N-methylpyrrole,5-carboxylic acid, $C_{11}H_{12}N_2O_2$: M.W. 204.35

An 11.0 g. (0.068 mole) quantity of 2,2'-bi-N-methylpyrrole in 40 ml. ether was added to 0.072 moles n-butyllithium in ether at -20° . The reaction mixture was warmed to room temperature, and then heated at the reflux temperature for seven hours. The reaction mixture was cooled to room temperature, and was poured onto an ether slurry of solid carbon dioxide. A yellow precipitate was

formed immediately, and was dissolved in water by the addition of 200 ml. cold water to the ether-precipitate mixture. The ether layer was extracted twice with 100 ml. water, and the combined water extracts acidified with twenty percent hydrochloric acid to a pH of four. A precipitate was obtained which was recrystallized from methanol-water to yield 6.0 g. (0.03 mole, 43%) of white crystalline product; m.p. 124-125°. The compound had a sharp carbonyl peak at 5.97 μ in the infrared.

Anal: Calculated for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.88; N, 13.72

Found: C, 64.90; H, 6.12; N, 13.23

2,2',5,2'',5'',2''-Tetra-N-methylpyrrole, $C_{20}H_{22}N_4$: M.W. 318.45

A 10.58 g. (0.066 mole) quantity of bi-N-methylpyrrole in 40 ml. ether was added to 0.066 moles of n-butyllithium in ether at -25° under a nitrogen atmosphere. The reaction mixture was warmed to room temperature, and heated at its reflux temperature for nine hours. Then 8.8 g. (0.066 mole) of anhydrous cupric chloride was added to the reaction mixture at -15°, and it was stirred at 0° for an additional two and a half hours. The light yellow reaction mixture turned a deep purple in color following the addition of the chloride salt. The reaction mixture was poured into 250 ml. of saturated aqueous ammonium chloride solution, and the product was isolated as described above for the other derivatives of bipyrrroles. After drying the reaction mixture, the ether and unreacted 2,2'-bi-N-methylpyrrole were removed by distillation under reduced pressure. The residue, a dark brown semi-solid, was dissolved

in ligroin, treated with Norite, and filtered to obtain a clear solution. The product was crystallized from the ligroin by cooling, and collected via filtration. The yield of pure product obtained was 0.75 g. (0.0024 mole, 7.1%) as a white powdery solid melting at 89-91°.

Anal: Calculated for $C_{20}H_{22}N_4$: C, 75.47; H, 6.92

Found: C, 75.41; H, 7.01

2,2'-Bifuryl-5-carboxaldehyde, $C_{12}H_6O_3$: M.W. 162.14

An ether solution of 2,2'-bifuryl was prepared by the addition of 6.9 g. (0.052 mole) of 2,2'-bifuryl to 150 ml. of anhydrous ether. The ether solution of bifuryl was cooled to -25°, and 0.057 mole of n-butyllithium in hexane was added during a half hour period. The reaction mixture was allowed to warm to room temperature, and then was heated at its reflux temperature for four hours. The reaction mixture was cooled to -30°, and 4.04 g. (0.055 mole) N,N-dimethylformamide in 30 ml. ether was added during ten minutes. A white precipitate was obtained. The reaction mixture was allowed to warm to room temperature during three hours, and then it was poured into an aqueous solution of ammonium chloride. The ether layer was separated from the water layer, and the water layer was washed twice with 75 ml. portions of ether. The combined organic layers were dried over anhydrous sodium sulfate. The ether solvent was removed by evaporation to yield 5.5 g. of crude product, m.p. 52-53°. The dark yellow crude material was recrystallized twice from methanol to obtain 5.0 g. (0.031 mole,

57.5 %) of pale yellow colored crystals, m.p. 53.6° . Literature value, m.p. 54° (5). The pure product showed an infrared carbonyl absorption at 5.92μ .

2,2'-Bifuryl-5-methyl ketone, $C_{10}H_8O_3$: M.W. 176.16

The lithium derivative of 5.4 g. (0.040 mole) 2,2'-bifuryl was prepared in the manner described under the synthesis of 2,2'-bifuryl-5-carboxaldehyde. Following the addition of 0.043 mole n-butyllithium in ether and refluxing for four hours, the reaction mixture was cooled to -30° , and 3.8 g. (0.043 mole) N,N-dimethylacetamide was added in 50 ml. anhydrous ether. The reaction mixture was stirred at room temperature for four hours, and the product isolation was as described in the synthesis of 2,2'-bifuryl-5-carboxaldehyde. The solvent was removed by evaporation to yield 3.8 g. crude product. A single recrystallization from methanol gave 3.4 g. (0.019 mole, 48.3 %) of bright yellow colored crystals; m.p. 50° . The product showed a sharp carbonyl absorption at 5.94μ in the infrared.

Anal: Calculated for $C_{10}H_8O_3$: C, 68.13; H, 4.55

Found: C, 67.97; H, 4.64

Attempted synthesis of 2-(2'-thienyl)-furan

Successive portions of 10.2 g. (0.15 mole) furan in 50 ml. ether and 12.6 g. (0.15 mole) thiophene in 50 ml. ether were added during a half hour at -20° to 0.30 mole n-butyllithium in 300 ml.

ether. The reaction mixture was allowed to warm to room temperature, and then was heated at its reflux temperature for four hours. The reaction temperature was then lowered to 0° , and 40.3 g. (0.30 mole) of anhydrous cupric chloride was added quickly. The reaction mixture was stirred at 0° for two and one half hours, and then poured into 500 ml. saturated ammonium chloride solution. The organic layer was separated from the aqueous layer, washed with 200 ml. portions of water twice, and dried over anhydrous sodium sulfate. The ether was removed by evaporation, and the residue was distilled under vacuum to obtain 1.85 g. (0.014 mole, 18.5 %) of pure 2,2'-bifuryl and 5.3 g. of crude 2,2'-bithienyl. The 2,2'-bithienyl was recrystallized from ligroin to obtain 4.6 g. (0.028 mole, 36.8 %) of 2,2'-bithienyl; m.p. 31.5° . Literature value, m.p. 32° (2).

Attempted synthesis of 2-(2'-furyl)-N-methylpyrrole

To an ether solution of 0.30 mole n-butyllithium in 200 ml. anhydrous ether was added 13.8 g. (0.18 mole) of N-methylpyrrole and 13.2 g. (0.18 mole) of furan in the stated order. Both heterocyclics were initially dissolved in 50 ml. ether before addition to the n-butyllithium solution which occurred at -20° during a period of an hour. The reaction mixture was warmed to room temperature, and then heated at its reflux temperature for six hours. The mixture was cooled to -20° , and 40.3 g. (0.30 mole) of anhydrous cupric chloride was added during a quarter of an hour. The reaction mixture was stirred at 0° for

three hours, and then poured into 450 ml. of aqueous ammonium chloride. The ether layer was separated and the water layer was washed twice with 100 ml. ether. The combined ether extracts and organic layer were dried over anhydrous calcium sulfate. The ether was removed by evaporation, and the residue was distilled under vacuum to obtain 4.54 g. (0.034 mole, 25 %) of pure 2,2'-bifuryl. No other product could be isolated from the residue, a dark semi-solid. The 2,2'-bifuryl was identified by means of infrared spectroscopy.

Attempted synthesis of 2,2'-bithienyl

The method of Ramanathan and Levine (6) was used to synthesize 0.2 mole of thienyllithium in 100 ml. anhydrous tetrahydrofuran. To this solution was added 42.0 g. (0.2 mole) of 2-iodothiophene dissolved in 90 ml. tetrahydrofuran at -15° during a half hour. The reaction mixture was allowed to warm to room temperature, and then it was heated at its reflux temperature for an hour. The mixture was poured into 300 g. crushed ice, and the organic phase was separated. The water layer was washed with two portions of 50 ml. ether, and the combined extracts and organic layer were dried over anhydrous sodium sulfate. The ether, tetrahydrofuran, and 25.6 g. (60 %) of the 2-iodothiophene were recovered by vacuum distillation. The residue was dissolved in 25 ml. of anhydrous ether, treated with Morite, and the ether was removed by evaporation. Light yellow crystals, 4.33 g. (equal to 32 % of the unrecovered 2-iodothiophene) of 2,5 diiodothiophene were recovered, m.p. $39-40^{\circ}$.

Literature value, m.p. 40.5° (9). The compound had an infrared spectrum which was identical to a known sample of 2,5-diiodothiophene.

Attempted synthesis of 2,2',5'-terthienyl

A solution of 0.2 mole of thienyllithium in 190 ml. anhydrous tetrahydrofuran was prepared as previously described in the attempted synthesis of 2,2'-bithienyl. The thienyllithium solution was cooled to -20° , and 22.6 g. (0.2 mole) of 2,5-dibromothiophene was added during a one half hour. The reaction mixture was allowed to warm to room temperature, and then it was heated at its reflux temperature for three hours. The product isolation procedure used here was that used on the 2,2'-bithienyl synthesis, except that the distillation residue, 22.6 g., was chromatographed on 140 g. of activated alumina. After eluting the column with 365 ml. of dry hexane in ten fractions, the hexane was removed by evaporation to yield 2.4 g. of unreacted 2,5-dibromothiophene and 7.2 g. 2-bromothiophene. This represents a total recovery of 32 %, as 10 % of the starting material and 22 % of 2-bromothiophene which could have been produced.

Attempted synthesis of 2,3'-bithienyl

To 16.8 g. (0.2 mole) thiophene in 100 ml. anhydrous tetrahydrofuran was added 0.23 mole n-butyllithium in hexane at -20° . The reaction mixture was stirred at -15° for two hours,

and then 16.3 g. (0.2 mole) 3-bromothiophene was added during one half hour after lowering the reaction mixture temperature to -70° . The reaction mixture was stirred at -70° for two and one half hours, and then allowed to warm to room temperature during two hours. The reaction mixture was poured into 200 ml. of a saturated aqueous solution of ammonium chloride, and then the resulting water layer was washed twice with 50 ml. portions of ether. The combined ether extracts and organic layer were dried over anhydrous sodium sulfate. The solvent was evaporated off, and the residue distilled under vacuum to obtain 14.6 g. 3-bromothiophene; representing a 90 % recovery of starting material. The recovered 3-bromothiophene had an infrared spectrum identical to that of the starting material.

2-Iodothiophene, C_4H_3IS : M.W. 260.09

Thianaphthelene, 26.8 g. (0.2 mole) in 100 ml. anhydrous ether, was reacted with 0.2 mole n-butyllithium in hexane at -10° . The reaction mixture was stirred for one hour at -10° to complete the reaction, and then 42.0 g. (0.2 mole) 2-iodothiophene was added to the mixture during one half hour. The reaction mixture was stirred at room temperature for twelve hours, and then poured into 150 ml. water. The water layer was extracted twice with 50 ml. portions of ether, and the combined extracts and organic layer dried over calcium chloride. The solvent was evaporated off, and the residue was distilled under vacuum to obtain 25.7 g. (62 % recovery) 2-iodothiophene, 14.9 g. (55 % recovery)

thianaphtholene, and 15.0 g. residue. The residue was dissolved in 35 ml. ligroin, treated with Norite, and cooled in an ice bath to obtain 10.7 g. yellow crystals, m.p. 58-59°. An additional recrystallization from hexane resulted in 10.2 g. (9.059 mole, 20 %) yellow plate-like crystals, m.p. 63-63.5°. Literature value, m.p. 63.4-65° (9).

N.M.R. SPECTRA

A Varian A-60 n.m.r. spectrometer operating at approximately 35° was used to obtain all n.m.r. spectra. The samples were run in thin walled A-60 sample tubes. Tetramethylsilane was used as the internal reference standard ($\tau = 10.00$).

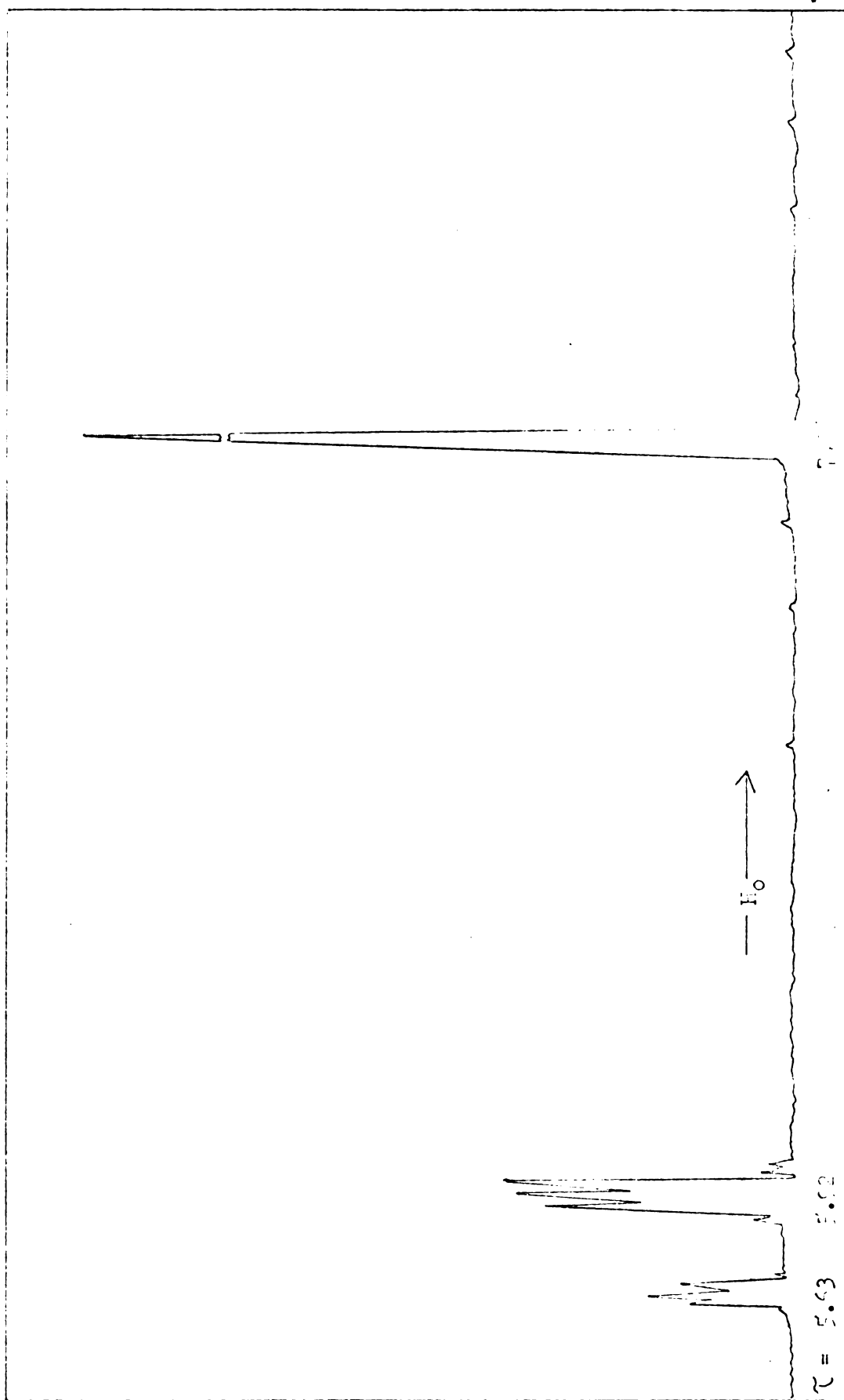


Figure 1. N.M.R. spectrum of 2,2'-bi-11-methylpyrrole, first, with sweep of 500 c.p.s.

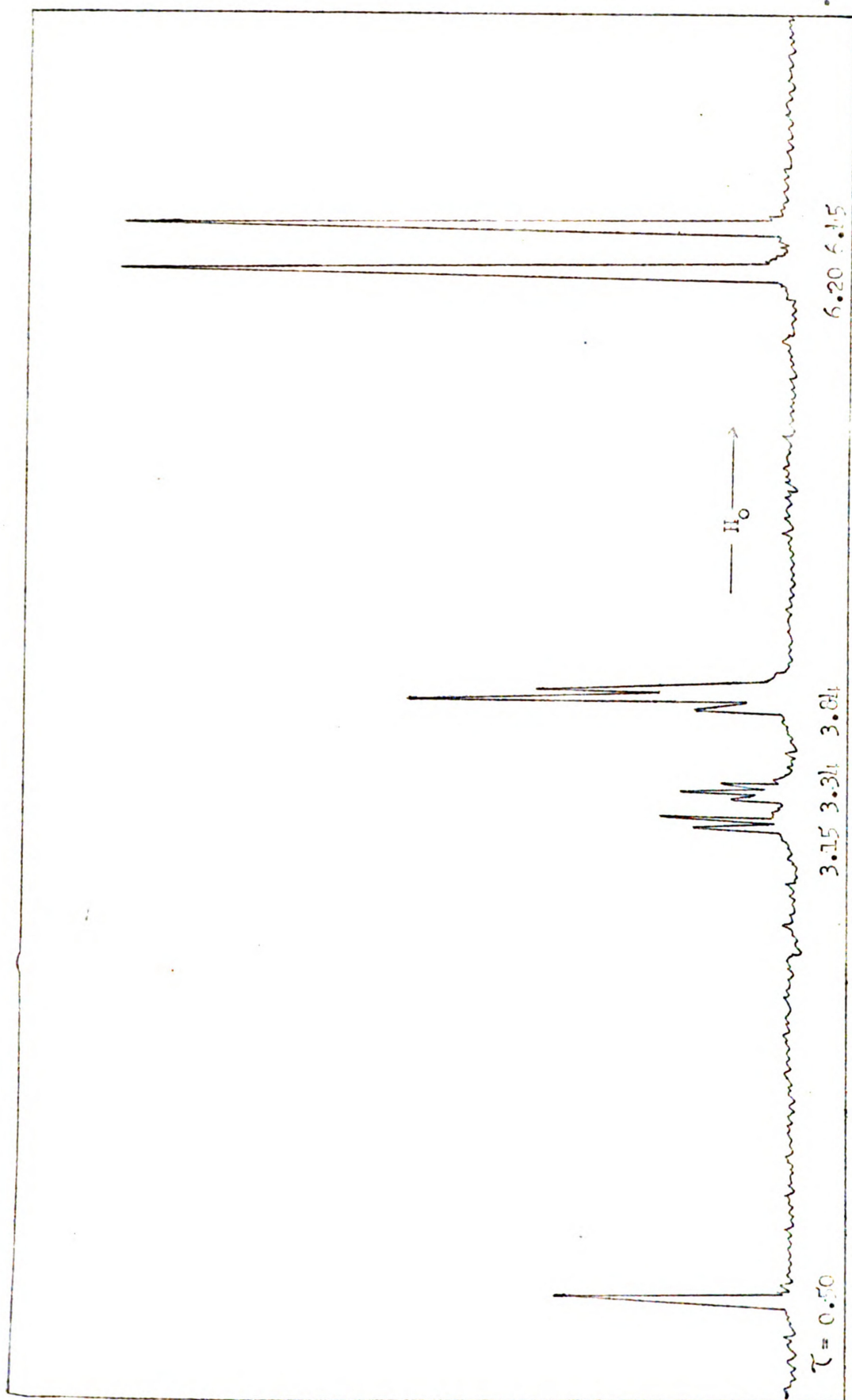


Figure 2. N.m.r. spectrum of 2,2'-bi-N-methylpyrrole-5-carboxaldehyde in CDCl_3 with sweepwidth 1000 c.p.s.

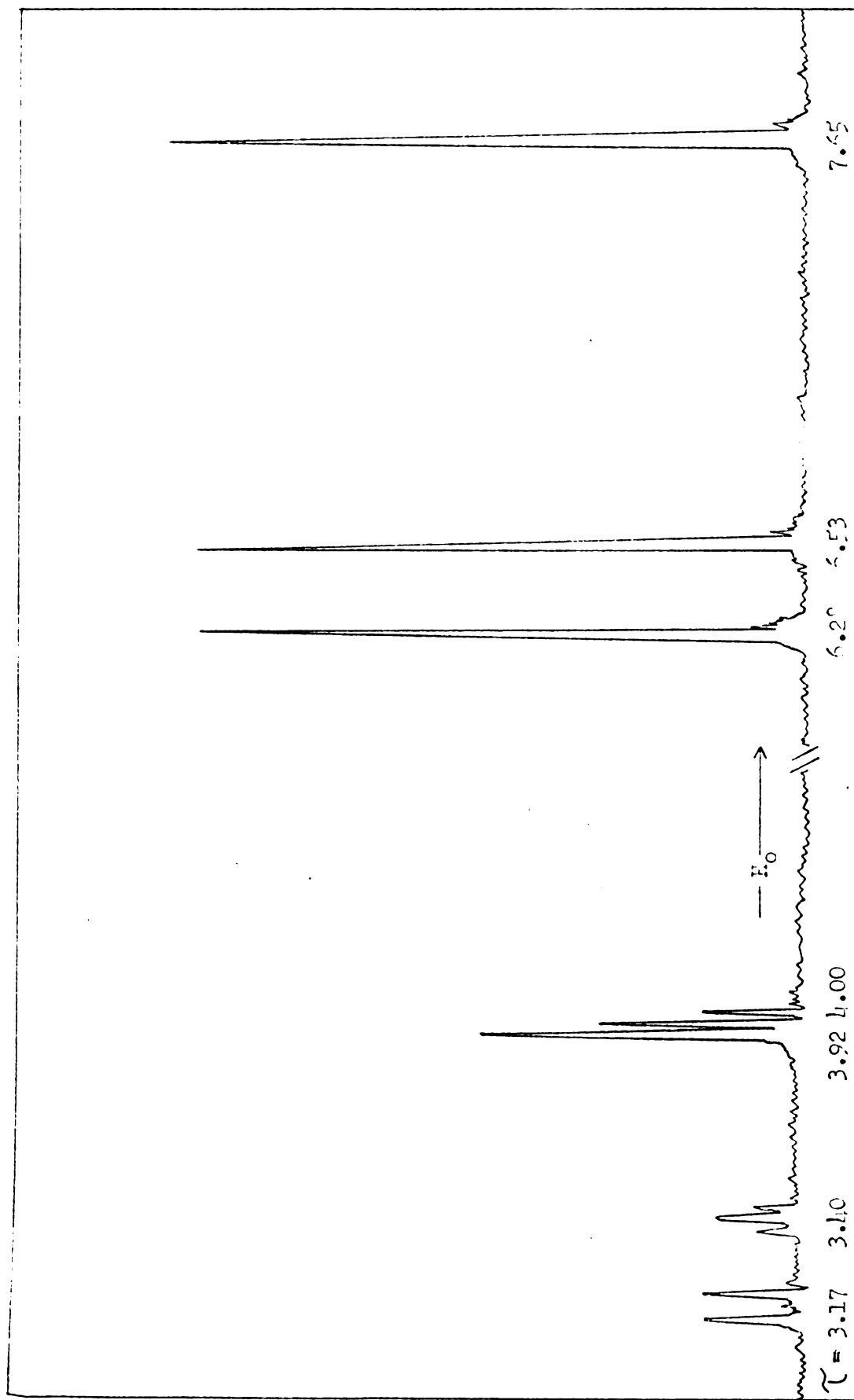


Figure 3. N.m.r. spectrum of 2,2'-bi-N-methylpyrrolid-5-one in CH_4 with sweep rate 500 c.p.s.

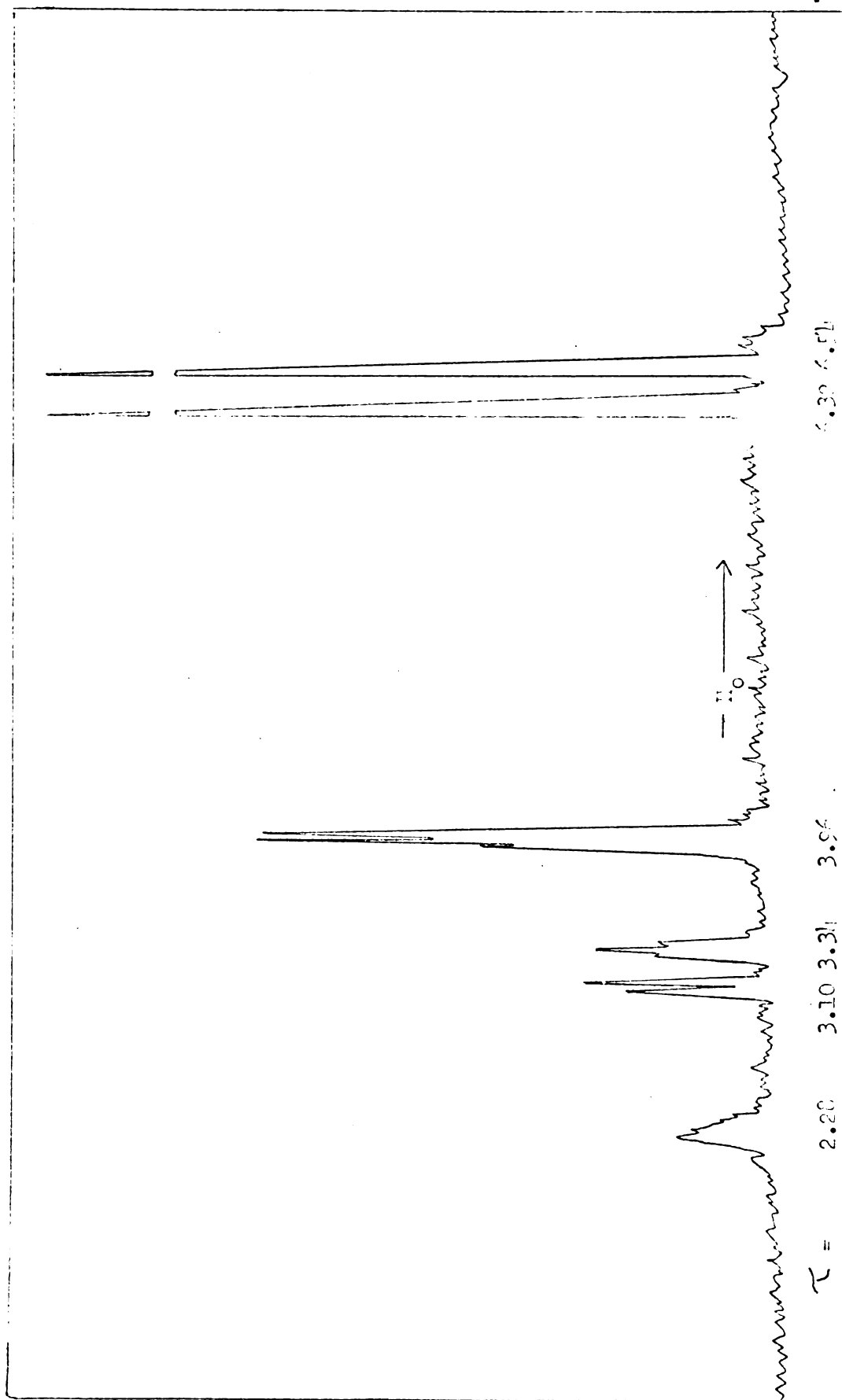


Figure 4. N.M.R. spectrum of 2,2'-bi-5-methylpyrrole-5-carboxylic acid in acetone with sweepwidth 1000 c.p.s.

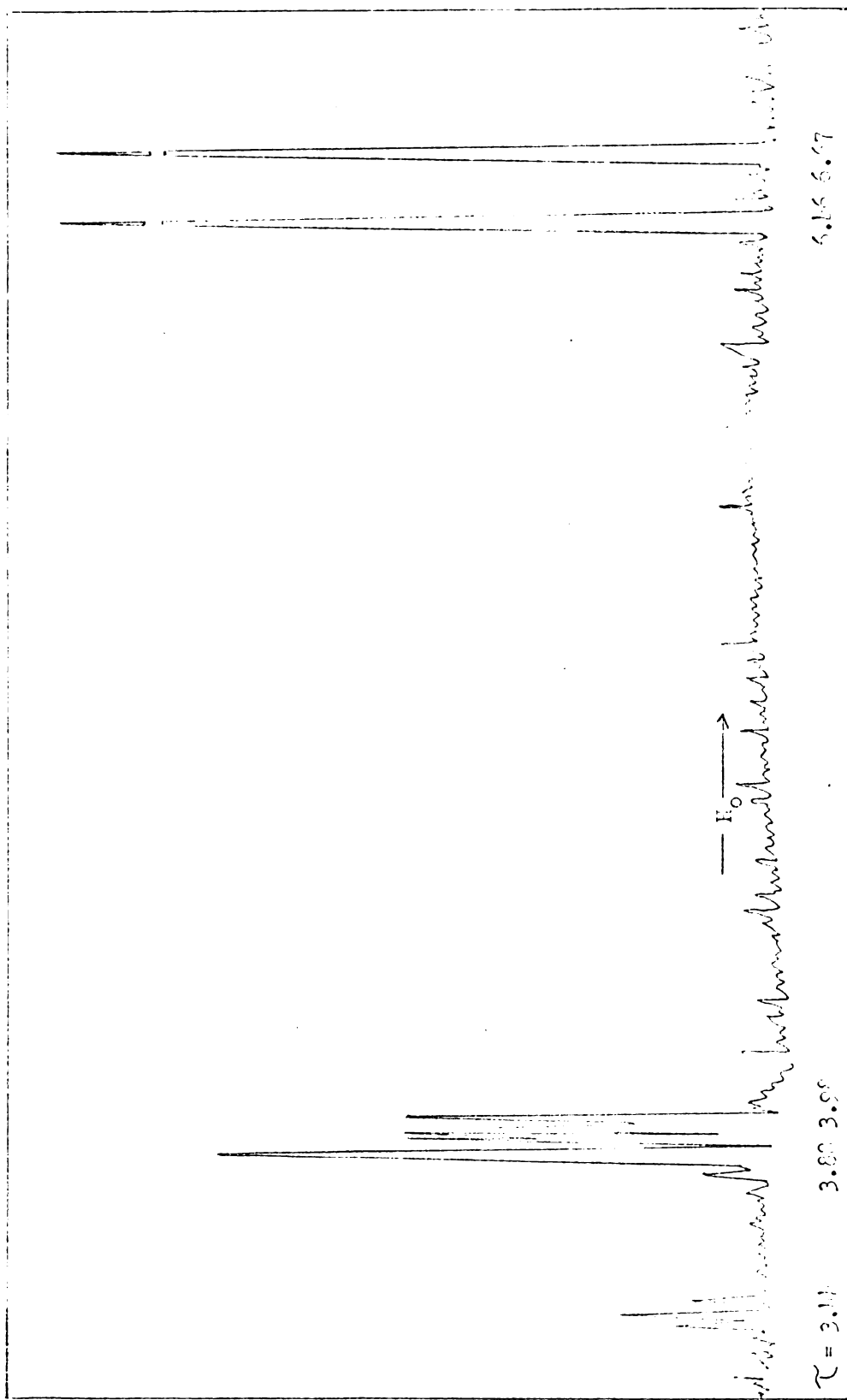


Figure 5. N.M.R. spectrum of 2,2',5',2'',5'',2'''-tetra-tert-butyl-1,4-benzodioxane in $CDCl_3$ with solvent peak at 7.04 ppm.

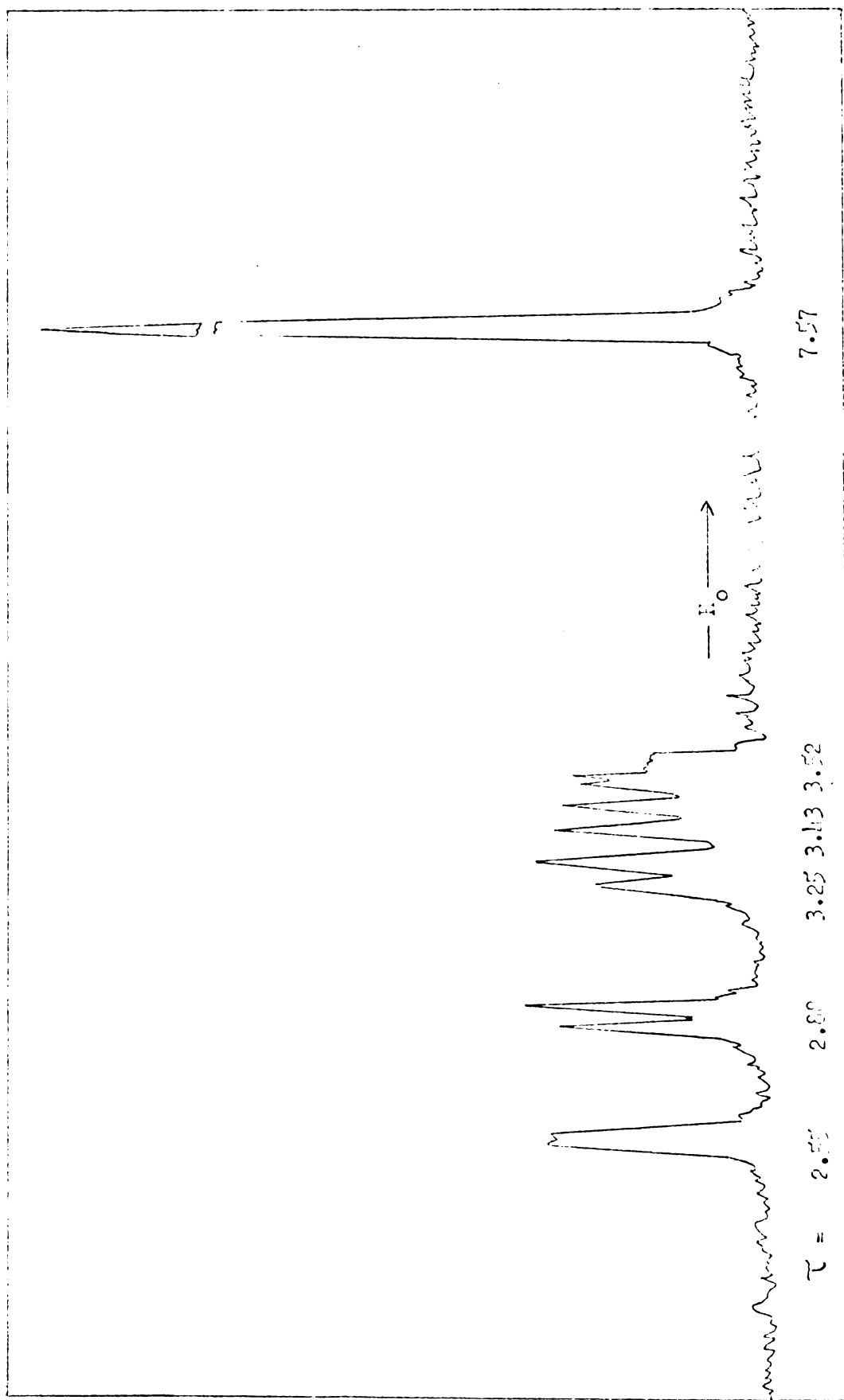


Figure 7. NMR spectrum of 2,2'-biphenyl-5-methyl ketone in CDCl₃ at 50°C.

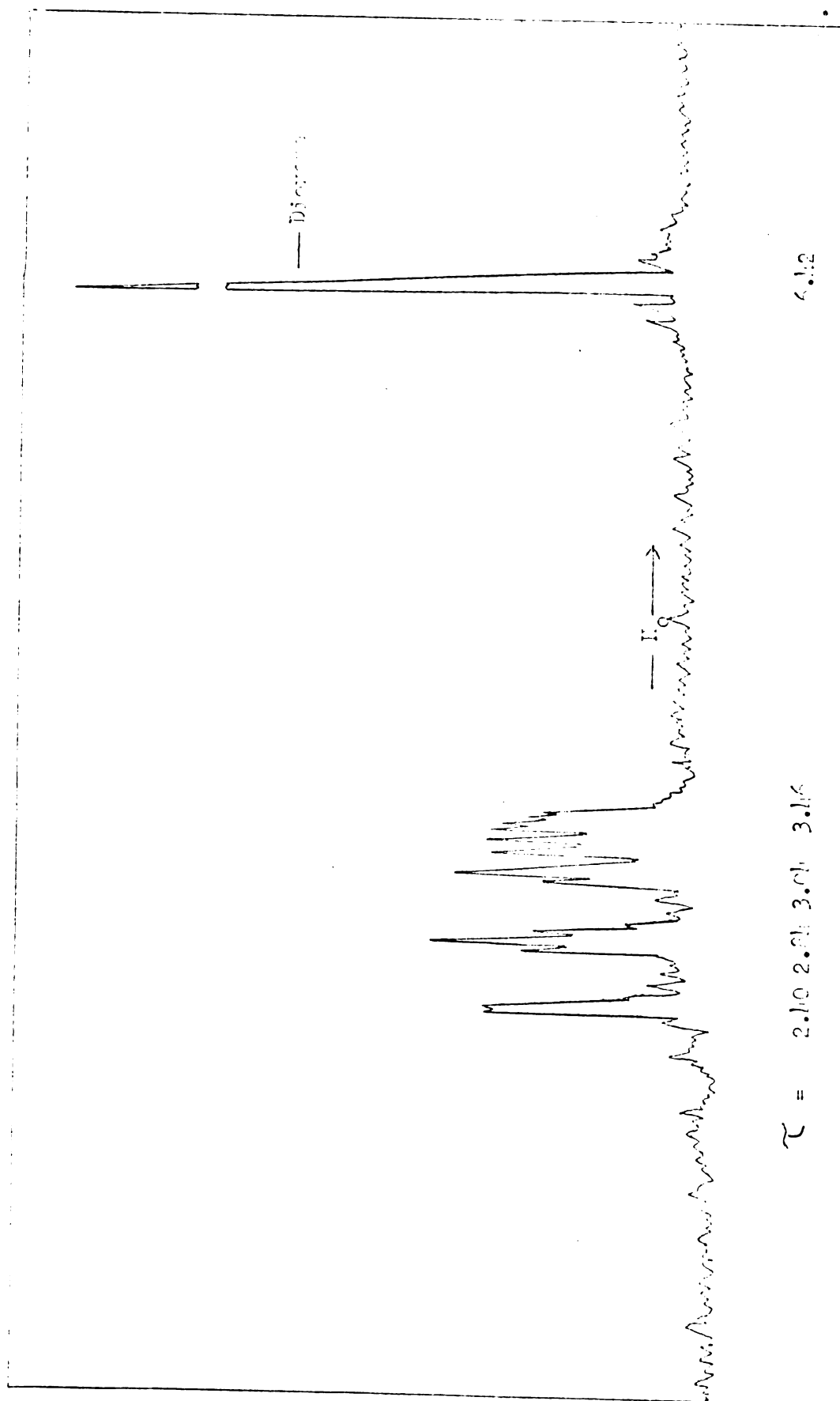


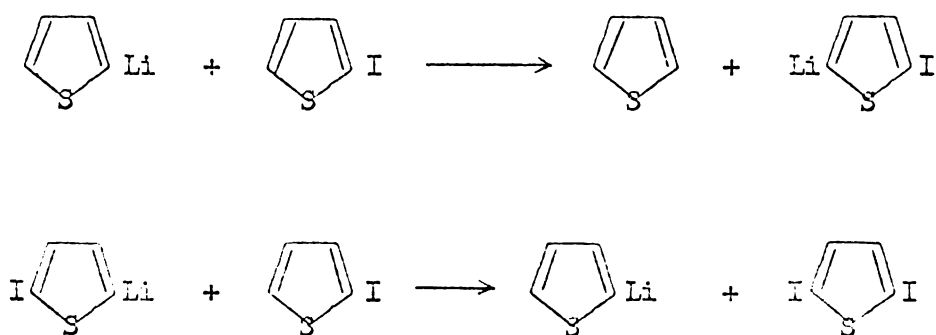
Figure 6. N.M.R. spectrum of 2,2'-difluoro-5,5'-carboxylic acid in dioxane at 100°C.

RESULTS AND DISCUSSION

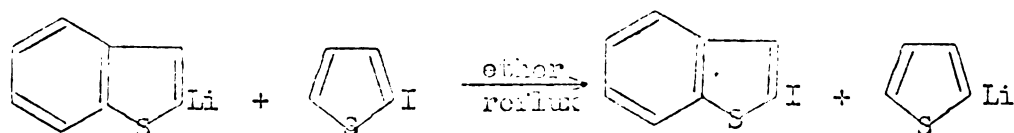
The alkylation and arylation of thiophene via the coupling of 2-thienyllithium and alkyl or aryl halides was carried out successfully by Levine and Ramanathan (6), with the best results obtained in anhydrous tetrahydrofuran as a reaction solvent. In the case of arylation, coupling occurred exclusively in tetrahydrofuran.

In the case of heterocyclic arylation, investigated in the present study, there was an exclusive preference for halogen-lithium exchange to occur. The above was indicated in the reactions between 2-thienyllithium and the heterocyclic halides, 2-iodothiophene and 2,5-dibromothiophene.

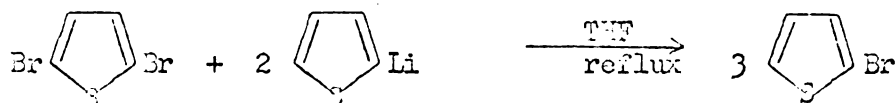
In the case of 2-iodothiophene, the only new species obtained was 2,5-diiodothiophene. An explanation for the formation of the latter product can be based on the following reaction sequence.



It is not difficult to see that the five position is activated toward nucleophilic attack due to the electron withdrawal inductive effect of the iodine. This activated position is then metalated by any 2-thienyllithium present. The resulting 2-iodo-5-lithium thiophene can then undergo metal-halogen exchange with additional 2-iodothiophene present in the reaction mixture. The fact that an iodoheterocyclic compound will undergo exchange was further evidenced by isolation of a twenty percent yield of 2-iodothianaphthalene from the reaction of molar quantities of 2-lithium thianaphthalene and 2-iodothiophene.



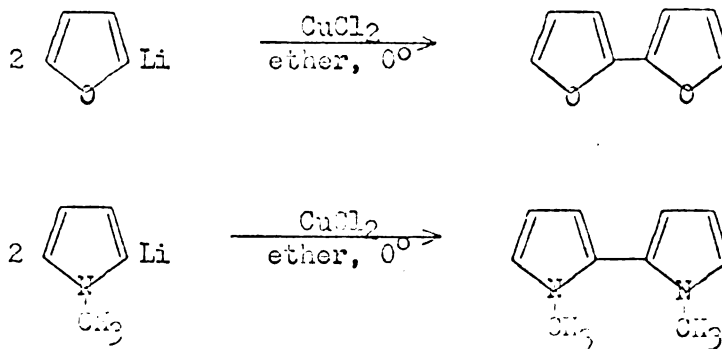
Additional studies with metal-halogen coupling reaction attempts indicated the same preference toward exchange with the bromoheterocyclic compounds. In the attempted synthesis of 2,2',5'-terthienyl from 2,5-dibromothiophene and 2-thienyllithium, the only compound isolated was 2-bromothiophene.



In the studies on the synthesis of 2,2',5'-terthienyl, a twenty two percent yield of the 2-bromothiophene was isolated from the reaction mixture.

An investigation was conducted to attempt a coupling of 3-bromothiophene and 2-thienyllithium. It was hoped that the less reactive 3 position on the thiophene nucleus would resist exchange and instead couple to give the unsymmetrical 2,3'-thienyl. The reaction gave only starting material back, indicating that exchange had not occurred. However, under the reaction conditions utilized, the 3-bromothiophene was also too unreactive to permit coupling.

A successful synthesis of symmetrical biheterocyclic systems was achieved with the use of anhydrous cupric chloride as a coupling agent. The compounds 2,2'-bifuryl and 2,2'-bi-N-methylpyrrole were obtained in a forty percent yield by the interaction between the heterocyclic lithium compound and the cupric salt.



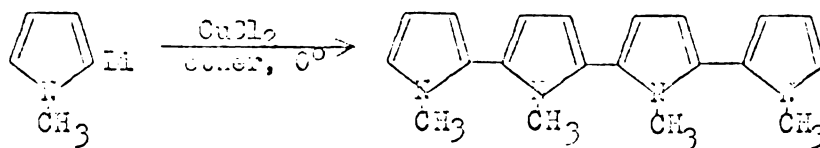
The advantage of this procedure lies in the high yields of the symmetrical biheterocyclic and the fact that the reaction involves a single step. All previous reported syntheses of 2,2'-bifuryl gave low yields and involved multi-step reaction sequences.

The reaction conditions were examined in an effort to determine optimum conditions. Results indicated that low temperatures and high dilution favored the production of the desired compounds by reducing the major competing reaction, polymerization. Ether was also found to be preferable over tetrahydrofuran as the solvent media.

Product	Solvent	Temp. (°C)	Conc. (M.)	% Yield
2,2'-Bifuryl	Ether	Reflux	1.25	7.0
"	Ether	Reflux	0.42	26.0
"	THF	Reflux	0.42	17.0
"	Ether	0	0.42	42.0
2,2'-Bi-N-methyl- pyrrole	Ether	Reflux	1.25	25.0
"	Ether	Reflux	0.42	28.0
"	Ether	0	0.42	42.0

This coupling procedure was extended to the synthesis of another symmetrical biheterocyclic system, 2,2'-bi-N-methylpyrrole. The lithium derivative of 2,2'-bi-N-methylpyrrole was treated with cupric chloride to obtain a seven percent yield of the

2,2',5',2'',5'',2'''-tetra-N-methylpyrrole.



Having obtained the biheterocyclic systems of 2,2'-bifuryl and 2,2'-bi-N-methylpyrrole in good yield, the 5 position biheterocyclic derivatives of each were synthesized by interaction with n-butyllithium. The lithium derivatives were then treated with a carbon dioxide-ether slurry, with N,N-dimethylformamide, and with N,N-dimethylacetamide to synthesize 2,2'-bifuryl-5-carboxylic acid, 2,2'-bifuryl-5-carboxaldehyde, 2,2'-bifuryl-5-methyl ketone, 2,2'-bi-N-methylpyrrole-5-carboxylic acid, 2,2'-bi-N-methylpyrrole-5-carboxaldehyde, and 2,2'-bi-N-methylpyrrole-5-methyl ketone. All of these products were obtained in yields varying from twenty-six to sixty-three percent. The derivatives of 2,2'-bifuryl were obtained in the higher yields. This may be rationalized as a function of the extent to which the individual biheterocyclic systems could be metalated. In previous studies on the metalation of furan and N-methylpyrrole, furan was metalated in substantially higher yields and under milder reaction conditions (7,8).

The N.M.R. spectra of the biheterocyclic derivatives were examined mainly to substantiate their structures. All the N.M.R. spectra of the 2,2'-bi-N-methylpyrrole derivatives and the N.M.R. spectrum of 2,2'-bifuryl-5-methyl ketone were

in agreement with the proposed structures. When an electron withdrawing group was in the 5 position of the 2,2'-bi-N-methylpyrrole nucleus, the methyl groups were located at different τ values. As a result, a hydrogen content of three could be assigned to the integrated methyl peaks, and from this assignment, the number of additional hydrogens in the molecule could be calculated. The hydrogen content checked out in all cases.

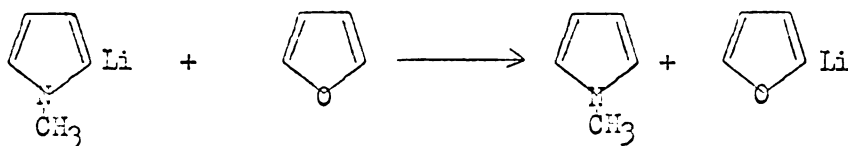
The N.M.R. spectrum of 2,2',5',2'',5'',2'''-tetra-N-methylpyrrole was used to substantiate the structure of this compound also. Assuming the proposed structure, two different methyl peaks should be present. Furthermore, the relative ratio of the integrated peak heights of the two peaks should be one to one, and will be one to one for only the proposed structure. This was found to be the case upon investigation of the spectrum.

In addition, the effect of the substituent groups on the biheterocyclics was investigated. As was anticipated, the electron withdrawing groups in the 5 position of the biheterocyclic molecules caused all hydrogen peaks to shift downfield in the N.M.R.

The use of cupric chloride as a coupling agent to obtain unsymmetrical biheterocyclic systems was also investigated. Assuming that equimolar quantities of 2-furyllithium and 2-thionyllithium were produced on the addition of cupric chloride, it seemed reasonable to expect a ratio of one to one to two of 2,2'-bifuryl, 2,2'-bithionyl, and 2-(2'-furyl)-thiophene to be obtained in the coupling reaction. However, the reaction mixture

was found to contain only 2,2'-bifuryl and 2,2'-bithienyl in a ratio of approximately one to two. The same coupling reaction was attempted with equimolar quantities of the lithium derivatives of furan and N-methylpyrrole. In this case, only 2,2'-bifuryl was isolated in a twenty-five percent yield.

The rational for these results may rest upon the relative stabilities of the metalated heterocyclics. In both of the reactions attempted, the most stable metalated compound was the one giving the majority of the isolated biheterocyclic. The majority of the least stable organo-metallic may have been used up as a metalating agent for any unreacted heterocyclic molecule present.



No attempt was made to isolate the starting materials in the reactions examined. One additional explanation for the failure to obtain unsymmetrical heterocyclic systems may be the ease with which the biheterocyclic molecule polymerizes under the reaction conditions employed. The unsymmetrical biheterocyclics may have been too unstable to survive.

SUMMARY

Two methods for the synthesis of symmetrical and mixed biheterocyclics were investigated. The first method involved a coupling between an aryllithium compound and arylhalide, but was found to be unsuccessful due to a preference for metal-halogen exchange. The second method, coupling of an aryllithium compound with anhydrous cupric chloride, lead to the synthesis of the symmetrical biheterocyclics 2,2'-bifuryl, 2,2'-bi-N-methylpyrrole, and 2,2',5',2'',5'',2'''-tetra-N-methylpyrrole. No mixed biheterocyclics could be synthesized with the cupric salt used as a coupling agent.

The lithium compounds of 2,2'-bifuryl and 2,2'-bi-N-methylpyrrole were prepared, and were used to produce several derivatives of these biheterocyclic compounds.

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