Tetrahedron, 1963, Vol. 19, pp. 1119 to 1126. Pergamon Press Ltd. Printed in Northern Ireland

PATHWAYS OF N-AMINOPYRROLE SYNTHESIS

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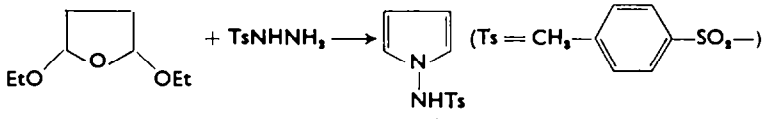
(*Received* 20 *November* 1962)

Abstract—Acid-catalyzed condensation of tosylhydrazine with 2,5-diethoxytetrahydrofuran yielded, in addition to N-tosylamidopyrrole, the bistosylhydrazone of succindialdehyde and two hydropyridazine derivatives; the composition of the product was highly dependent upon the choice of reaction conditions. On the basis of chemical and spectral evidence structures were established for all of these compounds, and their interconversions were studied.

N-TOSYLAMIDOPYRROLE (I) was required for a study of the chemistry of aminonitrenes.[1] Condensation of 2,5-diethoxytetrahydrofuran with tosylhydrazine was expected to yield I in a single step since analogous pyrrole syntheses employing ammonia and primary amines are well known.[2a] Careful choice of reaction conditions does indeed lead to I, but a variety of other substances can arise from the



I

same reactants. Presupposing that our observations are relevant to the general problem of N-aminopyrrole synthesis, we wish to record experiments which define the structures of these compounds and conditions for their formation and interconversion.

When ethanol containing hydrochloric acid (~1%) was chosen as the reaction medium, the mixture darkened even at room temperature and gave intractable tars. Substitution of a trace of phosphoric for the hydrochloric acid resulted in the formation of white crystals of the weakly acidic substance II, the bistosylhydrazone of succindialdehyde.[3] Spectral[4] and microanalytical data supported this structural assignment,

$$\text{TsNHN=CHCH}_2\text{CH}_2\text{CH=N—NHTs}$$

II

[1] D. M. Lemal, S. McGregor and T. W. Rave, to be published.

[2a] N. Elming in *Advances in Organic Chemistry: Methods and Results*, Vol. 2, pp. 100–102. Interscience, New York (1960). [b] *Ibid.* pp. 82, 105.

[3] Mono- and bishydrazones as well as dihydropyridazines are common products from reactions of hydrazines with γ-dicarbonyl compounds (R. C. Elderfield, *Heterocyclic Compounds*, Vol. 6, pp. 103–107. John Wiley, New York (1957)

[4] Except where stated otherwise, all N.M.R. spectra were measured in deuterochloroform containing hexamethyldisiloxane (9·94 τ) as internal standard.

in particular the close similarity of the U.V. spectrum of II ($\lambda_{max}^{CH_3CN}$ 228 mμ, ϵ 23,100) to that of the tosylhydrazone of isobutyraldehyde ($\lambda_{max}^{CH_3CN}$ 229 mμ, ϵ 13,500). Both tosylhydrazones displayed complicated proton magnetic spectra in deuterochloroform solution. These complexities had their origin in part in *syn-anti* isomerism about the carbon-nitrogen double bond,[5] and in part, apparently, in more subtle phenomena. It was found that the spectra of the corresponding anions in D_2O containing excess NaOD were much simpler and more easily interpretable. Whereas the dianion of II existed as a mixture of geometrical isomers in this medium (i.e. both *syn* and *anti* orientations of the hydrazone anions were discernible), the anion of isobutyraldehyde tosylhydrazone was present as a single species, presumably the *syn* isomer.[6,7]

Bubbling hydrogen chloride through a benzene solution of II caused precipitation of a white solid identified as the hydrochloride of tosylhydrazine, and the mother liquor afforded the pyrrole I in good yield. The structure of this substance, which formed a thermally-stable salt in dilute base,[1] was established by microanalysis and spectral data. Both I.R. and U.V. (λ_{max}^{EtOH} 222 mu, ϵ 15,800) spectra were consistent with the pyrrole structure, and the N.M.R. spectrum offered definite proof of its correctness. Apart from the resonances arising from the seven tosyl protons (methyl singlet at 7·56 τ and AB quartet for the ring protons with halves centered at 2·38 and 2·72 τ, J = 8 cps), there appeared only a pair of triplets corresponding in area to two protons apiece. Not surprisingly, the N—H proton did not appear in the spectrum, and the two sharply-defined 1:2:1 triplets centered at 4·02 and 3·63 τ, $J_{23} = J_{24} = 2$ cps, are clearly assignable to the C_3 and C_2 ring protons, respectively.[8]

It should be noted that the pyrrole I was also synthesized in one step from 2,5-diethoxytetrahydrofuran and tosylhydrazine by boiling with acetic acid under reflux, but that the yield of pure I was only 8%. When the acetic acid solvent was kept cold a new crystalline solid was isolated. The microanalysis, the U.V. spectrum (λ_{max}^{EtOH} 231 mμ, ϵ 11,200), and the I.R. spectrum, in particular the lack of N—H stretching absorption and the presence of a weak band ($\lambda_{max}^{CHCl_3}$ 6·15 μ) corresponding to C=N stretching, pointed to the expression III for the substance. As expected for this structure, the compound was converted to a salt by concentrated, but not by dilute hydrochloric acid, and not by aqueous alkali. The N.M.R. spectrum provided

[5] G. Karabatsos, J. D. Graham and F. M. Vane, *J. Amer. Chem. Soc.* **84**, 753 (1962).

[6] Consistent with these data is the fact that non-bonded repulsions in the *anti* configuration should be more serious for the isobutyraldehyde derivative than for II.

[7] It is of interest that the methine hydrogen of the isopropyl group underwent slow exchange with the medium (half-life of several days at room temperature), thus giving i. This was particularly

$$(CH_3)_2C(D)—CH=N—NHTs$$

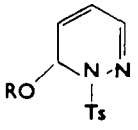
i

apparent from the gradual disappearence of the two doublets attributable to methyl and azomethine hydrogens and the concomitant appearance of singlets in their stead. The azomethine proton had suffered no measurable exchange after one and one-half weeks at room temperature. Hence the hydrazone anion *invariably* protonated on nitrogen.

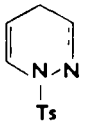
[8] The appearance of quartets instead of triplets in the spectrum of pyrrole itself is a consequence of spin coupling with the proton on nitrogen since pyrrole-N-d gives rise to triplets.*

* J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance* pp. 270, 271. McGraw-Hill, New York (1959).

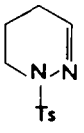
sufficient additional information to establish the structure firmly.[9] Besides the AB quartet with halves centered at 2·24 and 2·73 τ, J = 8 cps, corresponding to the aryl protons, the sharp singlet at 7·60 τ due to the aryl methyl, and the ethyl resonances centered at 8·85 τ (CH_3) and 6·28 τ (CH_2), there appeared a broad multiplet centered at ~3 τ,[10] a poorly-resolved triplet centered at 4·48 τ, J = 2·5 cps, and ill-defined absorption in the 7·8–8·8 τ region arising from four protons. The very low field multiplet, corresponding in area to one proton, is attributable to the azomethine hydrogen, and the triplet (of equal area) to the moderately unshielded methine hydrogen. It is not surprising that the high field (methylene) absorption is spread out and poorly defined in view of the non-equivalence of the four protons and the resulting multiplicity of spin-spin splittings.



III R = Et
IIIa R = Me



IV

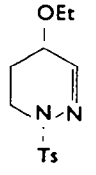


V

The presence of a nitrogen atom alpha to the ethoxyl group in III suggested that the latter function should be labile in acid under mild conditions, albeit less labile than the ether of a simple carbinolamine. Indeed, the action of cold methanol containing a trace of hydrochloric acid transformed III into IIIa. That no rearrangement had accompanied the exchange of alkoxyl functions was clear from the N.M.R. spectrum of IIIa and from the observation that this substance was easily reconverted to III with hydrochloric acid in ethanol.

Treatment of III with a cold, dilute solution of hydrochloric acid in glyme gave the pyrrole I in good yield, but the action of boron trifluoride in cold glyme transformed III in low yield into a new crystalline compound isomeric with the pyrrole. Structure IV[3,2b] was assigned this very weakly basic substance on the basis of solubility properties and spectral data. Absence of N—H stretching absorption on the I.R. spectrum coupled with the presence of weak C=N and C=C stretching bands ($\lambda_{max}^{CHCl_3}$ 6·14 μ and 5·99 μ, respectively) supported the proposed structure. The U.V. spectrum,

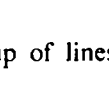
[9] The N.M.R. spectrum does not exclude the alternative possibility ii, but this structure is highly improbable on mechanistic grounds. Formation of ii in cold acetic acid would have required loss

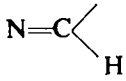


ii

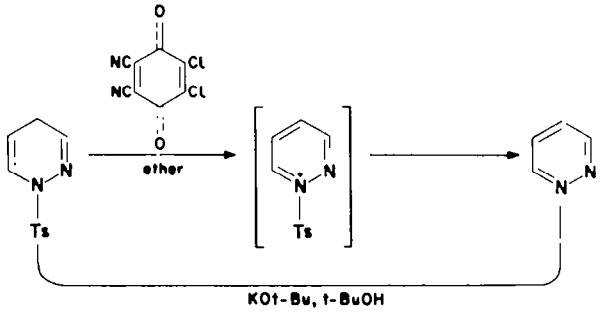
of ethanol from the intermediate III to give IV followed by double bond rearrangement and readdition of the alcohol from dilute solution. Using pure IV we were able to show that neither double bond rearrangement nor addition of ethanol occurred in the cold even when the solvent was ethanol (containing hydrochloric acid).

[10] G. Slomp (*J. Amer. Chem. Soc.* **84**, 673 (1962)) has recommended that the positions of multiplets whose origins are not discernible be reported in cps relative to a standard at specified spectrometer frequency. For the sake of clarity and consistency all multiplet positions are reported here in terms of the dimensionless parameter τ, but where the multiplicity is not well defined or difficult to analyze the apparent center, not the true origin, has been recorded. All spectra were recorded at 60 Mc.

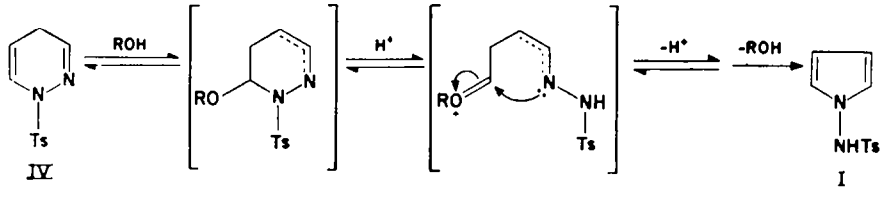
measured in ethanol, had maxima at 222 mμ, ε 10,700 and at 247 mμ, ε 6840. Again crucial evidence was provided by the N.M.R. spectrum, which eliminated from consideration the α,β-unsaturated hydrazone tautomer V. In addition to the lines arising from the protons of the tosyl group, the spectrum displayed three multiplets centered at 7·32, 5·11, and 3·15 τ corresponding in area to two, one, and two protons, respectively. The lowest field group of lines was assigned to the  and the

 hydrogens, the group of relative area one to the remaining, substantially less shielded vinyl hydrogen, and the high field group to the methylene hydrogens.

Degradative studies confirmed the correctness of expression IV for the isomer of pyrrole I. Potassium t.-butoxide in refluxing t.-butanol brought about elimination of *p*-toluenesulfinic acid from IV with the formation of pyridazine, identified by its highly characteristic U.V. spectrum and by its retention time in vapor phase chromatography. Treatment of IV with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in ether led again to pyridazine, identified as above.



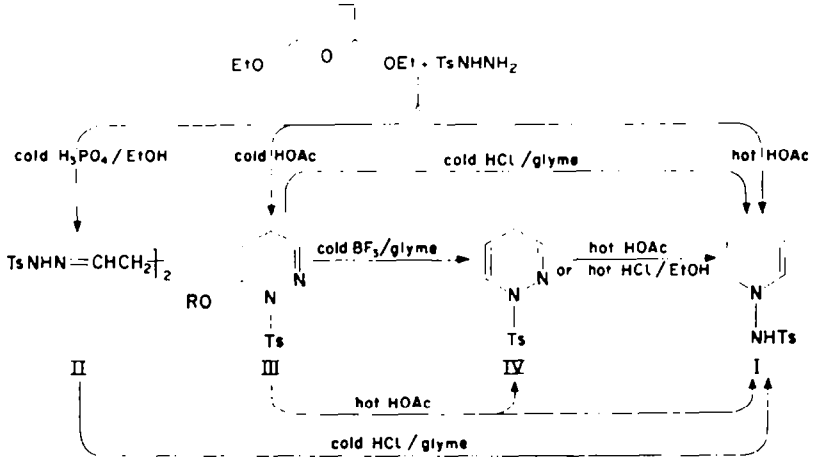
Like II and III, compound IV could be transformed into the pyrrole I, in this case through the agency of refluxing acetic acid or refluxing ethanol containing hydrochloric acid. The yields were substantially less than 20%, however, and it is significant that IV gave no pyrrole whatever when subjected to the action of hydrochloric acid in glyme under conditions which gave good yields with III the substrate. These facts make sense when it is borne in mind that conversion of the hydropyridazine system to the pyrrole system requires fission of the sulfonamide nitrogen-to-carbon bond. Whereas III is well suited for direct cleavage, IV presumably must undergo acid-catalyzed addition of ROH to the olefinic bond prior to C—N rupture:



Finally, hot acetic acid transformed III into a mixture of IV and I, the latter in higher yield (25% crude) than from pure IV (10% crude) under these conditions. Hence I was formed from III competitively with as well as via IV.[11]

The interrelationships among compounds I–IV are summarized in Chart 1. It is of interest that the conjugated dihydropyridazine V was never isolated notwithstanding the variety of reactions (Chart 1) which should have been conducive to its formation. Probably IV is the stabler tautomer.

Chart 1



EXPERIMENTAL

Mps were determined on a Kofler micro hot stage.

Succindialdehyde bistosylhydrazone (II)

In 100 ml 95% ethanol at 40° were dissolved 20·0 g (0·108 mole) tosylhydrazine (Aldrich) and 17·2 g (0·108 mole) 2,5-diethoxytetrahydrofuran (Columbia). Phosphoric acid (85%, 5 ml) was added, and the solution was allowed to stand at room temp for 2 hr. When cooled overnight in the refrigerator the solution deposited a white solid. Recooling the mother liquors in the refrigerator twice for 24 hr periods afforded two more crops of the same substance. If allowed to stand at room temp for 1 hr, this white solid turned yellow, but when it was suspended in carbon tetrachloride for 2 hr at room temp the liquid acquired a yellow color while the solid remained white. Apparently the carbon tetrachloride had dissolved an unstable impurity which was not isolated. Washed in this manner and recrystallized twice from ethanol, the combined solids (7·0 g, 15·4%) yielded white crystals, m.p. 139–140° (d). The I.R. spectrum in methylene chloride exhibited *inter alia* bands at 3·06 (N-H), 7·50 and 8·59 (sulfonamide), 9·25, and 10·96 μ. Found: C, 51·30; H, 5·25; N, 13·38; S, 14·94; Calc. for $C_{18}H_{22}N_4S_2O_4$: C, 51·19; H, 5·24; N, 13·26; S, 15·17%.

N-*Tosylamidopyrrole* (I) *from* II

In 80 ml benzene was dissolved 1·5 g (3·55 mmoles) of II, and anhydrous hydrogen chloride was bubbled through the solution for 1 hr while it was boiled under reflux. After another 1/2 hr heating was discontinued; the off-white powder which had precipitated was collected by filtration and

[11] With few exceptions throughout the series of reactions described in this paper, dark tars comprised a significant fraction of the products. The best route to I (25% overall, crude) proceeded via III, which was treated with glyme containing a trace of mineral acid as described earlier. Synthesis of the pyrrole via II (Chart 1) proved to be the most convenient pathway, and the overall yield was comparable though lower (18% crude).

dissolved in water. The aqueous solution was made barely basic with 5% NaOH and extracted 3 times with ether. Evaporation of the ethereal extracts gave 0·6 g (90·6%) tosylhydrazine, identified by m.p. and mixture m.p. with an authentic sample.

When the benzene filtrate from above was evaporated, 0·75 g (90%) brown solid was obtained. This was dissolved in 5% NaOH, and the filtered solution was acidified with conc. HCl. After several recrystallizations from benzene accompanied by treatment with Norit, the resulting light brown precipitate afforded 0·30 g (36%) of I as long white needles, m.p. 143–144°. The I.R. spectrum in chloroform exhibited characteristic bands at 3·05 (N-H), 7·34 and 8·53 (sulfonamide), 9·11, 9·21, 9·32, and 10·31 μ. Found: C, 55·65; H, 4·97; N, 12·15; S, 13·69; Calc. for $C_{11}H_{13}N_2SO_2$: C, 55·84; H, 5·12; N, 11·85; S, 13·56%.

N-*Tosylamidopyrrole* (I) *from tosylhydrazine and* 2,5-*diethoxytetrahydrofuran*

Tosylhydrazine (10 g; 53·8 mmoles) and 8·6 g (53.8 mmoles) 2,5-diethoxytetrahydrofuran were dissolved in 100 ml acetic acid. The solution was boiled 1 hr under reflux. Acetic acid (90 ml) was distilled (Vigreux column) from the deep red solution at 25 mm (35°), with the bath temp never above 60°. The residue was extracted 4 times with 100 ml portions of ether and the combined extracts were neutralized with solid sodium bicarbonate. Enough water was added to dissolve the sodium acetate which had precipitated. The organic layer was separated, washed twice with water, and dried ($MgSO_4$). Evaporation of the ether left a red oil which was extracted 5 times with 5% NaOH. Acidification of the combined extracts with conc. HCl caused 3·8 g (30%) brown solid to precipitate. Several recrystallizations from benzene accompanied by treatment with Norit gave 1·0 g (7·9%) of I (m.p. 142–144°).

3-*Ethoxy*-2-*tosyl*-2,3,4,5-*tetrahydropyridazine* (III)

a. Tosylhydrazine (10 g; 54 mmoles) and 8·6 g (54 mmoles) 2,5-diethoxytetrahydrofuran were dissolved in 30 ml acetic acid, and the mixture allowed to stand at room temp for 10 hr. The solution, which had gradually turned red, was then placed in the refrigerator for 2 weeks; orange crystals were deposited during this interval. Three recrystallizations from ethanol gave 4·6 g (30%) of III as white plates, m.p. 97·5–98°. The I.R. spectrum ($CHCl_3$) had characteristic bands at 3·32, 7·41 and 8·52 (sulfonamide), 8·12, 8·89, 9·01, 10·11, 10·92, and 11·90 μ. Found: C, 55·33; H, 6·30; N, 9·71; Calc. for $C_{12}H_{16}N_2SO_2$: C, 55·25; H, 6·42; N, 9·91%. Mol wt: Calc. 282·4; Found: 285 (isothermal distillation).

b. Tosylhydrazine (10 g, 54 mmoles) and 2,5-diethoxytetrahydrofuran (8·6 g, 54 mmoles) were dissolved in 50 ml acetic acid and the mixture boiled under reflux for 20 min. After cooling, the deep red solution was made slightly basic with 5% aq. NaOH and extracted 4 times with ether. The combined extracts were washed twice with water and dried ($MgSO_4$). Evaporation of the ether gave 7·0 g (46%) crude red solid. Several recrystallizations of this material from ethanol yielded white crystals identical with those from procedure *a* (m.p. 98–99°).

Interconversion of III *and* IIIa

Compound III (200 mg; 0·71 mmole) was dissolved in 15 ml methanol containing 5 drops of 5% HCl. The solution was allowed to remain at 25° for 24 hr and was then evaporated to dryness *in vacuo*. One recrystallization of the resulting white solid afforded 90 mg (47·3%) of white crystals, m.p. 98–100°. A mixture m.p. with III (m.p. 97·5—98°) showed a large depression and the I.R. spectrum was slightly different from that of III: IIIa has bands at 3·37, 3·52, 10·30 μ and lacks the 10·11 μ band of III. The N.M.R. spectrum of the new compound was similar to that of III except that the quartet and triplet attributable to the ethoxy group of III centered at 6·28 τ and 8·85 τ, respectively ($CDCl_3$), were replaced by a singlet at 6·56 τ (CCl_4) corresponding to a methoxyl function.

Compound IIIa (100 mg; 0·37 mmole) was dissolved in 15 ml ethanol containing 6 drops of 5% HCl, and the solution was allowed to stand overnight at 25°. Evaporation to dryness yielded a white solid which was shown to be III by mixture m.p. and its I.R. spectrum.

N-*Tosylamidopyrrole* (I) *from* III

In 20 ml glyme[12] were dissolved 2·0 g (7·04 mmoles) III and 1 ml 5% hydrochloric acid. After standing 2 1/2 days at room temp the yellow solution was made strongly basic with 5% NaOH, and

[12] The glyme (ethylene glycol dimethyl ether) used in this and subsequent experiments had been distilled from $LiAlH_4$.

most of the glyme was swept off with a stream of nitrogen. The basic solution was boiled with Norit, filtered, and acidified with conc. HCl. The resulting light brown precipitate (1·4 g, 84%) was identified as the pyrrole (I) by its characteristic I.R. spectrum.

1-*Tosyl*-1,4-*dihydropyridazine* (IV) *from* III

Compound III (1 g; 3·55 mmoles) was dissolved in 18 ml glyme;[18] anhydrous boron trifluoride was bubbled through the stirred solution very slowly for 45 min at room temp. Stirring was continued for 1 hr. The resulting yellow solution was brought to pH 7 with 5% NaOH and extracted 4 times with ether. Evaporation of the combined ethereal extracts gave 0·7 g yellow oil which was chromatographed on 60 g Grace silica gel, grade 950. The column was eluted successively with benzene, benzene–chloroform (4:1), benzene–chloroform (3:2), benzene–chloroform (2:3), benzene–chloroform (1:4), and chloroform. Benzene–chloroform (3:2) eluted 0·10 g (11·7%) IV as a white solid, which melted at 113–115° (d) after 2 recrystallizations from ethanol. The I.R. spectrum measured in chloroform displayed *inter alia* bands at 3·26, 6·13, 7·3 and 8·46 (sulfonamide), 8·18, 8·23, 8·82, and 11·11 μ. Found: C, 55·67; H, 4·94; N, 11·70. Calc. for $C_{11}H_{12}N_2SO_2$: C, 55·84; H, 5·12; N, 11·85%.

Pyradizine from IV

a. Compound IV (20 mg; 0·084 mmole) was dissolved in 6 ml anhydrous ether and the solution was cooled to 0-5° in an ice bath. 2,3-Dichloro-4,5-dicyano-1,4-benzoquinone (21 mg, 0·092 mmole) in 6 ml anhydrous ether was added dropwise and the yellow solution stirred in the cold for 15 min. After the solution had warmed to room temp during 25 min stirring, 5 ml water was added and agitation continued for 15 min. The water layer was separated and its U.V. spectrum measured. This spectrum was identical with that of authentic pyridazine in water.[13]

The aqueous solution (2 ml) was diluted with 8 ml water and the pH was adjusted to ~1 with conc. HCl. After 2 ether extractions to remove any organic by-products, the water solution was evaporated to dryness with a stream of nitrogen. The resulting orange film was dissolved in 2 ml anhydrous methanol and neutralized with silver oxide. The oxide was removed by filtration; the orange solution was concentrated to 0·04 ml. Vapor phase chromatography of the solution on a 2 ml column packed with Ucon Polar on acid-washed Chromosorb P gave a peak with retention time identical to that of authentic pyridazine.

b. In 10 ml of t.-butanol were dissolved 30 mg (0·71 mmole) potassium metal and 25 mg (0·11 mmole) IV; the solution was boiled under reflux 3 1/2 hr. The U.V. spectrum of the reaction mixture indicated the presence of pyridazine. Evaporation yielded a yellow solid which was extracted with water, and the extract was again taken to dryness. Anhydrous methanol (2 ml) was added, and the presence of pyridazine in the resulting solution was confirmed as in procedure a by vapor phase chromatography.

N-*Tosylamidopyrrole* (I) *from* IV

a. A solution of 0·35 g (1·47 mmoles) IV in 10 ml acetic acid was boiled under reflux 1 hr. After cooling, the golden solution was adjusted to pH 7 with aqueous sodium hydroxide and extracted 4 times with ether. When the combined ethereal extracts had been evaporated to dryness 150 mg brown solid remained. The solid was partially dissolved by 8 ml 5% NaOH, the mixture was filtered, and the filtrate was acidified with conc. HCl. Two ether extractions gave 63 mg (18%) light yellow solid which, after 2 recrystallizations from ethanol, afforded 20 mg (5·7%) white crystals identified as the pyrrole (I) by the I.R. spectrum.

b. Compound IV (100 mg; 0·42 mmole) was dissolved in 16 ml hydrochloric acid-in-ethanol (1%). The mixture was boiled 1 hr under reflux and the resulting yellow solution was made very basic with 5% NaOH. Most of the ethanol was swept off with a stream of nitrogen. After 2 ether extractions to remove any base-insoluble compounds, the residual solution was acidified with 5% HCl and again extracted twice with ether. A yellow solid (50 mg) remained when the combined ethereal extract was evaporated to dryness. The solid was dissolved in 5% NaOH; the solution was treated with Norit and then filtered. Acidification gave a precipitate (10 mg, 10%; m.p. 141–143°) identified as I by mixture m.p. with the authentic pyrrole.

[18] R. C. Evans and F. Y. Wiselogle, *J. Amer. Chem. Soc.* **67**, 61 (1945).

N-Tosylamidopyrrole (I) *and 2-tosyl-2,5-dihydropyridazine* (IV) *from* III *in acetic acid*

Compound III (7·2 g; 25·4 mmoles) was dissolved in 80 ml acetic acid and the solution boiled under reflux for 25 min. The red solution was cooled, neutralized with aq. NaOH and extracted 4 times with ether. A dark brown solid (2·7 g) remained after evaporation of the combined extracts. The I.R. spectrum of this substance indicated the presence of both I and IV. Consequently, the solid was triturated with 30 ml 5% NaOH; the undissolved material (1·5 g) was identified as IV by its I.R. spectrum. Recrystallization gave 1·0 g (16·7%) of pure IV (white crystals, m.p. 113–115°).

Acidification with conc. HCl of the basic aqueous extract from above yielded 1·5 g (25%) of brown solid. Several recrystallizations from benzene afforded I, identified by its m.p. (142–144°) and I.R. spectrum.

Acknowledgement—The authors wish to express their appreciation to the National Institutes of Health for generous financial support.