[CONTRIBUTION FROM THE DEPT. OF ORGANIC CHEMICAL DEVELOPMENT, ELI LILLY AND CO.]

# Synthesis of Amides of Lysergic Acid[1]

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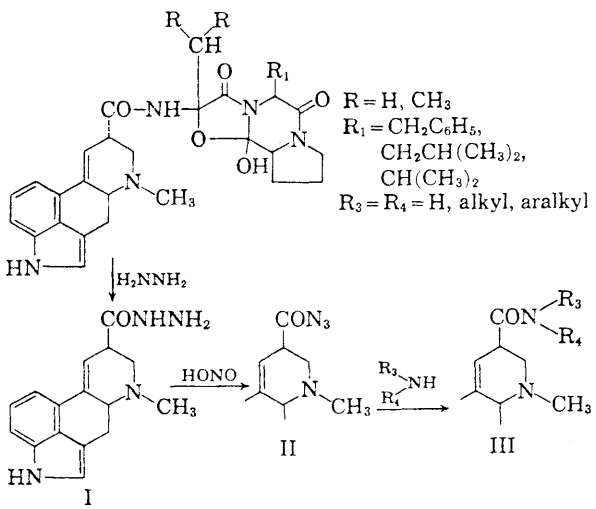
Although interest in the chemistry and pharmacology of lysergic acid derivatives has remained high for many years, until recently only one useful method for converting lysergic acid into its amide derivatives has been recorded. This method as described by A. Stoll[2] consists of cleaving ergot alkaloids with hydrazine. The resulting lysergic acid hydrazide on treatment with nitrous acid is converted into the azide which may be used to prepare the desired amide by acylation of an appropriate amine.




Although this procedure is frequently capable of producing amide product in good yields, certain inherent difficulties reduce its practical value. Of these, the most important is that the necessary reaction conditions for preparing lysergic acid hydrazide result in a racemized and isomerized material, DL-isolysergic acid hydrazide. Further, the method leaves much to be desired in terms of operational ease since the azide must be collected in a relatively large volume of ether and several hours are required to carry out the acylation step.

Because optically active +-lysergic acid is readily available through aqueous alkaline cleavage of ergot alkaloids,[3] a method which utilized the free acid and caused no racemization was desired. The classical methods for preparing amides by acylation of amines with esters or acid chlorides fail when applied to lysergic acid. Thus, while the methyl[3] and ethyl[4] esters of lysergic acid are known, they fail to undergo aminolysis except in the special case already mentioned involving the use of hydrazine. On the other hand, attempts to prepare lysergic acid chloride yield only decomposition products.

Numerous new amide-forming techniques, chiefly arising from work in the peptide field, have appeared in the recent literature. Many of these were investigated with respect to lysergic acid amide synthesis. A method to be suitable for this application must operate under mild non-acidic conditions because of the sensitive nature conferred upon lysergic acid derivatives by their indole containing structure.

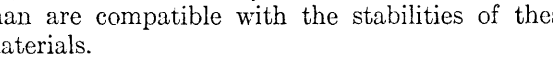
Most of the newer methods involve the application of certain mixed anhydrides. Such techniques frequently suffer from one or more of the following disadvantages:

(*a*) The reaction fails to go to completion.

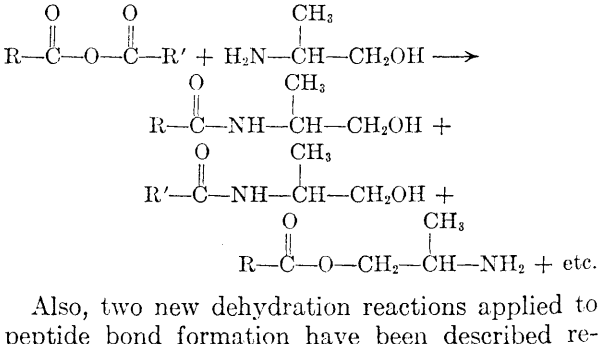
(*b*) The reaction requires higher temperatures than are compatible with the stabilities of these materials.

(*c*) The reacion system decomposes lysergic acid or its amide product because of the acidic character.

(*d*) The mixed anhydride undergoes disproportionation which contributes to reaction incompletion and/or nonspecific acylation:



(*e*) The mixed anhydride acylates in a nonspecific manner, resulting in a mixture of acylated products including esters, as well as amides where possible:



Also, two new dehydration reactions applied to peptide bond formation have been described recently, wherein an acid and an amine are caused to condense under the influence of the powerful dehydration reagents, dicyclohexylcarbodiimide and ethoxyacetylene.

(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, New York, N. Y., September, 1957.

(2) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, 26, 944 (1943).

(3) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 104, (1934).

(4) A. Stoll and Th. Petrzilka, *Helv. Chim. Acta*, 140, (5) 1953).

J. Org. Chem 24 (1959) 368-72

Most of the methods examined, together with the general results obtained, are listed in Table I.

TABLE I

REACTION SYSTEMS APPLIED TO LYSERGIC ACID AMIDE SYNTHESIS

A. Mixed Anhydride Systems

| Mixed Anhydride | Value of System |
|---|---|
| R—$CON_3$[a] (II) | Poor. Required starting material was racemized in preparation |
| RCOCl[b] | None. Lysergic acid decomposed |
| $RCO_2COCF_3$[c] | Good. Non-specific acylation[d] |
| $RCO_2CO_2C_2H_5$[e] | None. Yielded ethyl lysergate |
| $RCO_2PO_2C_6H_4$[f] | Poor. Low yield with decomposition |
| $RCO_2SO_2C_6H_4CH_3$[g] | None. Decomposed lysergic acid |
| $RCO_2SO_2CH_3$[h] | Fair. Moderate yield with some decomposition |
| $RCO_2SO_3$[i] | Excellent in all respects |

B. Dehydration Systems

$$RCO_2H + H{-}N\begin{matrix}R_1\\R_2\end{matrix} \xrightarrow[\text{Reagent}]{-H_2O} RCON\begin{matrix}R_1\\R_2\end{matrix}$$

| Reagent | |
|---|---|
| $C_6H_5{-}N{=}C{=}N{-}C_6H_5$[j] | None. Very poor yield |
| $C_2H_5O{-}C{\equiv}CH$[k] | None. Very poor yield |

[a] A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943). [b] A. Stoll and A. Hofmann, U. S. Pat. **2,090,430** (1937). [c] E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952). [d] R. P. Pioch, U. S. Pat. **2,736,728** (1956). [e] R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951). [f] G. W. Anderson and R. W. Young, *J. Am. Chem. Soc.*, **74**, 5307 (1952). [g] J. H. Brewster, *J. Am. Chem. Soc.*, **77**, 6214 (1955). [h] No previous reference found. [i] G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2069 (1952). [j] J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955). [k] J. F. Arens, *Rec. trav. chim.*, **74**, 769 (1955).

Of the methods studied, the use of the mixed anhydride of sulfuric acid and lysergic acid proved most practicable because the difficulties inherent in the other method were absent. Thus, assays for total amide produced indicated that this reaction proceeded to completion. There was no decomposition observed which could be ascribed to the reaction, since it took place readily at low temperature and at no time was the system acidic in character. Disproportionation was not encountered and no evidence of esterification was observed. The amide products were obtained free from racemization. Further, the process was carried out rapidly and with considerable experimental ease.

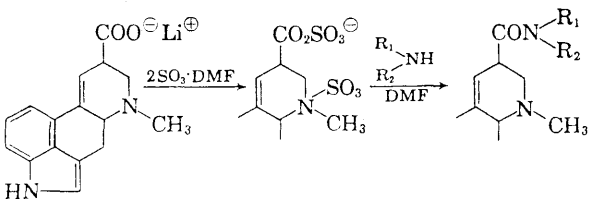
However, the yields of amide product isolated by this method were often considerably below theoretical as a consequence of the difficulties encountered in the isolation of these sensitive materials. In addition, the yield of lysergic acid amide is affected by the ever present equilibrium between the physiologically active lysergic acid series and the inactive isolysergic acid series. This equilibrium is a consequence of the possible chair conformation of ring D. Lysergic acid was deduced to possess an equatorial carboxyl group and isolysergic acid an axial carboxyl group.[5]

Fortunately, from a preparative standpoint, the amides of lysergic acid can usually be obtained as crystalline maleate or tartrate salts, while the amides of isolysergic acid generally fail to form such crystalline salts and remain in the mother liquors. Also, the equilibrium frequently favored the lysergic acid side and further amounts of it were often obtained through re-equilibration of the iso-material in the mother liquors. Thus, in spite of the difficulties cited, it was possible to obtain first crop yields of ergonovine maleate of 65%, with further amounts available through isomerization of the iso amide which remained in the mother liquor.

The stoichiometry of the reaction and the conditions necessary for its successful application were found of considerable interest. The best procedure was to dissolve +-lysergic acid monohydrate with an equivalent amount of lithium hydroxide monohydrate in methanol. The methanol was removed *in vacuo* and the residue of lithium lysergate was dissolved in dimethylformamide. A suitable amount of dimethylformamide was then distilled from the solution under reduced pressure to ensure that it was anhydrous.

The dry lithium lysergate solution was then chilled in an ice bath and a dimethylformamide solution containing two molar equivalents of sulfur trioxide was added quickly while mixing mechanically. Shortly thereafter, the reaction mixture was treated with five molar equivalents of the desired amine and then within a few minutes more a large amount of water was added and the amide product was isolated by extraction.

The success of the reaction depends very critically on the degree of adherence to the correct stoichiometry. It was for this reason that lithium hydroxide monohydrate was used, since it is nonhygroscopic and may be weighed accurately. Other alkali and alkaline earth hydroxides functioned as well but were less convenient to handle. Two molar equivalents of sulfur trioxide were required for each mole of lysergate anion, one forming the mixed anhydride and the other reacting with the piperidine nitrogen. Small deviations from the indicated ratio of sulfur trioxide to lysergate anion




(5) J. B. Stenlake, *J. Chem. Soc.*, 1626 (1955).

resulted in large decreases in the yield of amide product. Similarly, amounts of amine less than four to five molar equivalents resulted in decreased yield.

Two observations suggest that the piperidine nitrogen is complexed by the sulfur trioxide preferentially to its involvement in mixed anhydride formation: first, the stoichiometrical requirement already described, and second, the fact that the amide product can be isolated from the reaction mixture only after adding water which causes a fairly exothermic reaction to take place. This latter reaction was, doubtlessly, the hydrolysis of the sulfur trioxide complex of the tertiary nitrogen.

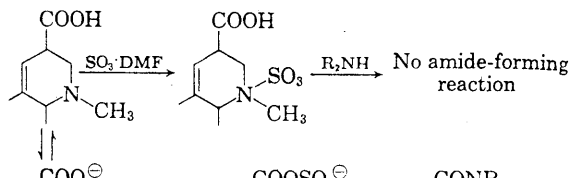
The reaction sequence was carried out very quickly since all three steps, anhydride formation, acylation, and hydrolysis, were virtually instantaneous. Reaction times from a few seconds to several hours did not materially affect the yield. Also, the reaction sequence was found to be little dependent upon temperature, proceeding well at temperatures from −20 to 35°.

Since the present work was aimed primarily towards finding a method for making the lysergic acid amide of an amino alcohol, L-2-amino-1-propanol, the fact that esters of lysergic acid were not formed from the anhydride of lysergic acid and sulfuric acid was unexpected. Not only could no trace of ester be found in this reaction, but treatment with simple alcohols failed completely to yield esters of lysergic acid.

The use of a suitable complex of sulfur trioxide was necessary to mask the extremely reactive nature of this compound and provide a convenient means of handling, storing, and measuring the reagent. Similar compounds with tertiary amines, such as *N*-ethylmorpholine or triethylamine, were found to bind the sulfur trioxide so strongly as to make it unavailable for reaction with the lysergate anion. The less stable complex with dioxane provided sulfur trioxide for reaction but was more difficult to prepare and use.

The sulfur trioxide-dimethylformamide adduct possesses nearly ideal characteristics. It readily provides sulfur trioxide for mixed anhydride formation, its solutions in excess dimethylformamide are stable in the cold for months, and dimethylformamide is the most useful solvent found for reactions involving lysergic acid. The adduct is a nicely crystalline, low melting solid which can be isolated and recrystallized from acetonitrile without decomposition.

The reaction of free lysergic acid with sulfur trioxide and subsequent treatment with excess amine gave poorer yields of amide product than those obtained with lysergate anion. Furthermore, the reaction followed a different course as was indicated by the stoichiometry. The free acid gave better yields when only one molar equivalent of sulfur trioxide was employed. The explanation probably may be found in the fact that lysergic acid, being a fairly typical amino acid, exists to some extent as the zwitterion. A representation of the reaction course is indicated below:




Although the early work was carried out using freshly prepared sulfur trioxide which was then distilled twice from phosphorus pentoxide, subsequent experimentation indicated that commercial sulfur trioxide could be added to dry dimethylformamide to give a reagent of high quality suitable for this synthesis.

## EXPERIMENTAL

*Sulfur trioxide-dimethylformamide complex.*[6] A carefully dried, 22-liter, round bottomed flask, fitted with an ice water cooling bath, condenser, dropping funnel, and mechanical stirrer, was charged with 10 to 11 l. of dimethylformamide (freshly distilled under reduced pressure). The condenser and dropping funnel were both protected from atmospheric moisture. Two lb. of sulfur trioxide[7] were then introduced dropwise very cautiously with stirring during 4 to 5 hr. The temperature was kept at 0–5° throughout the addition. After the addition was complete, the mixture was stirred for 1–2 hr. until some separated, crystalline sulfur trioxide–dimethylformamide complex had dissolved.

The reagent was then transferred to a suitable storage vessel, such as an automatic buret system with an adequate reservoir, and kept in the cold. While the initially colorless reagent gradually becomes first yellow and then dark orange in color during storage, its efficacy remains unimpaired for at least 3 to 4 months.

The molarity of the reagent was estimated by titration. An aliquot, first diluted with a little water to convert the sulfur trioxide into sulfuric acid, was titrated to a phenolphthalein endpoint with standard aqueous alkali solution. The molarity ranged from 1.00 to 1.15.

*The preparation of lysergic acid amides. General procedure.* A solution of 7.15 g. of +-lysergic acid monohydrate (25.0 mmol.) and 1.06 g. of lithium hydroxide hydrate (25.0 mmol) in 200 ml. of methanol was prepared. The solvent was distilled on the steam bath under reduced pressure. The residue of glass-like lithium lysergate was dissolved in 400 ml. of anhydrous dimethylformamide. About 200 ml. of dimethylformamide was distilled at 15 mm. pressure through a 12-in. helices-packed column. The resulting anhydrous solution of lithium lysergate in dimethylformamide was cooled to 0° and, with stirring, treated rapidly with 50.0 ml. of $SO_3$-DMF solution (1.00 molar). The mixture was stirred in the cold for 10 min. and then 125.0 mmol. of the desired amine was added. The stirring and cooling were continued for 10 min. longer when 400 ml. of water

(6) The sulfur trioxide-dimethylformamide complex is hereinafter referred to as $SO_3$-DMF.

(7) Commercially available as "Sulfan B" from the General Chemical Division, Allied Chemical and Dye Corp.

was added to decompose the reaction complex. After mixing thoroughly, 200 ml. of saturated aqueous saline solution was added. The amide product was then isolated by repeated extraction with 500 ml. portions of ethylene dichloride. Tests with Van Urk reagent were used to indicate completeness of extraction.

The combined extract was dried and then concentrated to a sirup under reduced pressure. It was usually good practice to avoid heating the extract or the sirup during the concentration.

The lysergic acid amide was ordinarily isolated in a crystalline form from the sirup as a salt (maleate, tartrate, etc.), which usually crystallized readily from methanol–ether solvent mixtures. Occasionally, the product could be isolated crystalline as the free base. Sometimes it was necessary to resort to chromatography.

*Lysergic acid-N-benzyl amide acid maleate.* A solution of 1.62 g. of potassium +-lysergate monohydrate (5 mmol.) in 25 ml. of anhydrous dimethylformamide was prepared and carefully protected from contact with moisture. The solution was chilled in an ice water bath and then treated quickly with 7.7 ml. of $SO_3$-DMF solution, providing 10.0 mmol. of $SO_3$. The mixture was chilled with swirling for 5 min. and then 2.68 g. of benzylamine (25.0 mmol.) was added. After 5 min. more cooling and swirling, 100 ml. of 20% saline solution was added. The mixture was extracted with ethylene dichloride. The completeness of extraction was determined with Van Urk reagent. The fifth 150-ml. extract gave only a slightly blue color with the reagent.

The combined extracts were dried briefly with anhydrous magnesium sulfate and then concentrated to a sirup *in vacuo*. Care was taken to avoid heating the residual sirup. The residue was dissolved in 25 ml. of methanol, the solution made slightly acid with maleic acid and then treated with ether to a slight turbidity. After chilling for 48 hr., the product, which had crystallized in rosettes of fine, nearly colorless needles, was collected, washed with a little fresh, cold methanol-ether mixture (1:1), and dried. The crude product weighed 1.80 g.

The +-lysergic acid-*N*-benzyl amide acid maleate was purified by recrystallization from methanol and ether for characterization as follows: $[\alpha]_D^{25}$ +17.2° (*c*, 1 in methanol); m.p. 193° (dec.).

*Anal.* Calcd. for $C_{23}H_{23}N_3O.C_4H_4O_4$: C, 68.48; H, 5.74; N, 8.87. Found: C, 68.45; H, 5.83; N, 9.09.

*Ergonovine acid maleate.* A solution of 7.60 g. +-lysergic acid dihydrate (25.0 mmol.) and 1.06 g. of lithium hydroxide hydrate (25.0 mmol.) in 200 ml. of methanol was prepared. The solvent was distilled on the steam bath under reduced pressure. The residue of lithium lysergate was dissolved in 400 ml. of anhydrous dimethylformamide. About 200 ml. of dimethylformamide was distilled at 15 mm. pressure through a 12-inch helice-packed column. The resulting anhydrous solution of lithium lysergate in dimethylformamide was cooled to 0° and, with stirring, treated rapidly with 50.0 ml. of $SO_3$-DMF solution (1.00 molar). The mixture was stirred in the cold for 10 min. and then 9.40 g. of L-2-amino-1-propanol (125 mmol.) was added. The stirring and cooling were continued for 10 min. longer when 400 ml. of water was added to break the reaction complex. The mixture was acidified with tartaric acid and extracted with chloroform (three 500-ml. portions) to remove most of dimethylformamide. The aqueous mixture was treated with 80 g. of sodium chloride and 200 ml. of ethanol. The mixture was then layered with 500 ml. of ethylene dichloride and made basic with concentrated ammonium hydroxide solution. After being mixed thoroughly, the ethylene dichloride layer was separated and extraction continued with fresh portions of ethylene dichloride until all the amide product had been extracted as indicated by tests with Van Urk reagent.

The extract was concentrated *in vacuo* keeping the mixture cold at all times. The residue of sirup was collected in 50 to 75 ml. of methanol, filtered, and acidified with solid maleic acid. The solution was then carefully layered with 50 ml. of ether. After several minutes, crystallization was well under way. The mixture was treated with 200 ml. of ether and refrigerated for several hours. The crop of colorless, fine needles was collected on a Buchner funnel, washed with a cold methanol-ether mixture (1:1), and dried. The ergonovine maleate thus obtained weighed 6.75 g. (61.5%) and was identical in all respects with an authentic sample of the naturally-occurring alkaloid.

Alternatively, the free base as the stable, crystalline addition compound, ergonovine-chloroform,[8] could be isolated by triturating the residue from the ethylene dichloride extract with cold chloroform.

The crystallization mother liquor contained mainly the acid maleate of the isolysergic acid amide, ergonovinine. After removing the solvent under reduced pressure, the residue was treated with 200 ml. of 10% aqueous saline solution and excess concentrated ammonium hydroxide solution. The free base was extracted with ethylene dichloride. The extract was evaporated under diminished pressure and the residual sirup was treated with 100 ml. of alcohol and 10 ml. of 4*N* 1:1 aqueous alcoholic potassium hydroxide. This mixture was kept at room temperature for 1 to 2 hr. and then neutralized with solid carbon dioxide. After adding 400 ml. of ether, the mixture was filtered and the filtrate was concentrated. The sirup remaining was treated in the manner previously indicated for the isolation of ergonovine maleate. The second crop weighed 0.91 g. (8.3%). Further crops may be isolated by recycling the iso-material through the alkaline equilibration procedure.

Alternatively, the residual iso-material from the ethylene dichloride extract could be isolated as the crystalline ergonovinine nitrate.[9]

*N-Cyanomethyl-+-lysergic acid amide.* The mixed anhydride from 3.70 g. of lysergic acid hydrate, prepared as for ergonovine above, was treated with excess cyanomethylamine. After decomposing the complex with 400 ml. of saturated saline solution, the product was extracted with three 500-ml. portions of chloroform. The combined extracts were dried (anhydrous magnesium sulfate) and then concentrated under diminished pressure. The residual sirup was dissolved in 30 ml. of methanol, acidified with solid maleic acid, treated to turbidity with ether, and refrigerated for several hours. The precipitate of colorless, soft needles was collected, washed with cold ether-methanol mixture (2:1), and then dried at 50° *in vacuo*. The product weighed 2.52 g. A portion of the material was recrystallized from methanol and ether solvent mixture for analysis: $[\alpha]_D^{25}$ +42.9° (*c*, 1 in methanol); m.p. 194° (dec.) (corr.).

*Anal.* Calcd. for $C_{18}H_{18}N_4O.C_4H_4O_4.{}^1/_2H_2O$: C, 61.17; H, 5.48; N, 12.97. Found: C, 61.25; H, 5.70; N, 13.03.

*Lysergic acid anilide.* Potassium +-lysergate monohydrate (1.62 g., 5.0 mmol.) was dissolved in 25 ml. of anhydrous dimethylformamide. The solution was treated with 8.20 ml. of $SO_3$.DMF solution (1.21 molar) and then chilled in an ice water bath for 20 min. when 2.30 g. of aniline (25 mmol.) was added. The mixture was swirled briefly and kept cold for 1 hr. After adding 100 ml. of 10% aqueous saline solution, the amide product was extracted with ethylene dichloride until no further amount of Van Urk-positive material could be extracted. The combined extract was concentrated under reduced pressure and the sirupy residue was dissolved in 20 ml. of methanol, acidified with maleic acid, and then treated with 200 ml. of ether. After being refrigerated for several days, the crystals were collected, washed free of sirupy material with 1:1 methanol-ether mixture, and air dried. The slightly off-white product weighed 0.48 g.

The combined mother liquor and washes were concen-

(8) A. Stoll and A. Hofmann, *Z. physiol. Chem.*, Hoppe-Seyler's, **251**, 155 (1938).

(9) S. Smith and G. M. Timmis, *J. Chem. Soc.*, 1166 (1936).

trated to a sirup under reduced pressure and the residue of sirup was treated with 150 ml. of 1.0*M* methanolic potassium hydroxide. After standing for 2 hr. at room temperature, the mixture was diluted with 400 ml. of 10% aqueous saline solution and the Van Urk positive material was extracted with ethylene dichloride. The residue from the extract, after conversion to the acid maleate, yielded 0.30 g. of lysergic acid anilide acid maleate. A portion of the combined crops of product was recrystallized from methanol, yielding fine colorless needles; m.p. 200° (dec.); $[\alpha]_D^{25}$ +43.8° (*c*, 0.5 in ethanol).

*Anal.* Calcd. for $C_{22}H_{21}N_3O.C_4H_4O_4$: C, 67.96; H, 5.48; N, 9.15. Found: C, 68.34; H, 5.76; N, 9.11.

*Ethyl +-lysergate.* Potassium lysergate (3.0 g., 9.25 mmoles) was dissolved in 10 ml. of dry dimethylformamide. The solution was chilled and then 1.1 g. of ethyl chloroformate (10 mmol.) was added. The mixture was kept cold for 30 min. when 0.90 g. of morpholine (10.3 mmol.) was added. After 30 min. longer, the cold mixture was added to 50 ml. of ice water, causing a yellow, unstable solid to separate. The solid was collected in chloroform and dried with anhydrous magnesium sulfate. After evaporating the chloroform, the residue of brown sirup was dissolved in a few milliliters of methanol. The solution was then acidified with maleic acid, treated to turbidity with ether, and refrigerated for several days. The product, ethyl +-lysergate acid maleate, was obtained in the form of fine, yellow needles, which were collected, washed free of tarry material with methanol-ether solvent mixture (1:1), and dried. The needles weighed 0.78 g., m.p. 155–160° (dec.). Recrystallization from methanol and ether gave massive prisms, faintly yellow in color, m.p. 155–157° (dec.).

*Anal.* Calcd. for $C_{18}H_{20}N_2O_2.C_4H_4O_4$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.19; H, 5.84; N, 6.92.

*Ergonovine maleate preparation via the methanesulfonic acid anhydride.* Lysergic acid monohydrate (1.43 g., 5.0 mmol.) was suspended in 25 ml. of dry dimethylformamide. The mixture was chilled to 0° and a cold solution of methanesulfonic acid anhydride in dry dimethylformamide (31.4 ml. of 0.35 molar solution) was added. The lysergic acid dissolved and after 30 min. in the cold, 2.2 g. of L-2-amino-1-propanol (20 mmol.) was added. The mixture was kept cold for 1 hr. and then worked up for ergonovine in the usual manner. The yield of ergonovine maleate was 0.55 g.

*Acknowledgment.* I wish to thank Dr. A. L. Kranzfelder and Dr. G. H. Svoboda for many helpful discussions during the course of this work. Also, appreciation is due Mr. H. L. Bird for paper chromatographic analyses, Mr. W. L. Brown for microanalyses, Dr. H. A. Rose for X-ray diffraction data, and Dr. H. E. Boaz for infrared spectra and microtitration data.

INDIANAPOLIS, IND.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

# Aldehydes Derived from 1,2,5-Trisubstituted Pyrroles

RICHARD RIPS AND N. P. BUU-HOÏ

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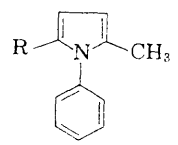
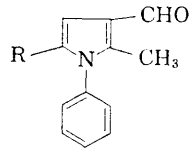
The formylation of 1-phenyl-2,5-dimethylpyrrole and 1,2-diphenyl-5-methylpyrrole was effected by means of dimethylformamide and phosphorus oxychloride, to give the corresponding monoaldehydes; 1-phenyl-2,3,5-trimethylpyrrole and 1,2-diphenyl-4,5-dimethylpyrrole were prepared by reduction of these aldehydes, and were also successfully formylated. A dialdehyde was also obtained from 1-phenyl-2,5-dimethylpyrrole.

In the framework of a general study on the chemical and pharmacological properties of substituted *N*-arylpyrroles,[1] we have investigated the behavior of 1-phenyl-2,5-dimethylpyrrole (I) and 1,2-diphenyl-5-methylpyrrole (II) toward dimethylformamide in the presence of phosphorus oxychloride. The formylation of a large number of derivatives of pyrrole had already been performed and the nucleus found to be highly reactive in that respect,[2] but *N*-arylpyrroles had not yet been investigated.

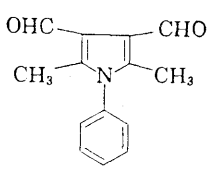


I, R = $CH_3$
II, R = $C_6H_5$

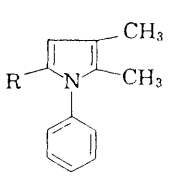


III, R = $CH_3$
IV, R = $C_6H_5$

Both pyrroles I and II readily underwent formylation to give 1-phenyl-2,5-dimethylpyrrole-3-aldehyde (III) and 1,2-diphenyl-5-methylpyrrole-4-aldehyde (IV) respectively, the best results being obtained when a diluent such as toluene was used for the reaction. In the case of 1-phenyl-2,5-dimethylpyrrole, small amounts of the corresponding *dialdehyde* (V) could also be isolated. The fact that 1,2-diphenyl-5-methylpyrrole, unlike I, gave no dialdehyde, points to a deactivating influence on the 3-position exerted by the 2-phenyl radical, and this effect justifies the assignment of structure IV to the formylation product of II. Wolff-Kishner reduction of aldehydes III and IV using Huang-



V



VI, R = $CH_3$
VII, R = $C_6H_5$

(1) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, in press.

(2) *Cf.* H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 145.