chloric acid, water, 10% sodium carbonate solution, and again water, dried, and distilled. The product, which was obtained in 66% yield (128 g.), boiled at 136° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3. Found: C, 69.0; H, 6.4.

Oxidation to terephthalic acid. A mixture of 2 g. of (V), 1 g. of sodium carbonate, 8 g. of potassium permanganate, and 100 ml. of water was refluxed for 30 min. The solution was filtered and acidified; yield of terephthalic acid, 1.2 g. (76%). The product was identified by the mixed m.p. of its dimethyl ester with an authentic specimen.

Methyl p-(α-isopropoxyethyl)-phenylacetate. A mixture of 192 g. of V, 224 g. of aluminum isopropoxide, and 1500 ml. of isopropyl alcohol was heated in a column in the usual manner, until no more acetone appeared in the distillate. Then the excess isopropyl alcohol was distilled off and the residue treated with 700 ml. of water, 400 ml. of concentrated hydrochloric acid, and 50 ml. of benzene. The product was extracted with ether; it boiled at 140–160° (0.05 mm.) and, on redistillation, at 148° (0.05 mm.). Its yield was 135 g. (57%).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.2; H, 8.5. Found: C, 71.4; H, 8.3.

Methyl p-(α-hydroxyethyl)-phenylacetate (VI). In the manner described for the preparation of III (R = OH), 192 g. of V in 600 ml. of ether was reduced with 10 g. of sodium borohydride in 50 ml. of methanol. The product (153 g., 79%) boiled at 144° (2 mm.).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 68.2; H, 7.6.

Methyl p-vinylphenylacetate (*as* II). In the manner described above, 19.5 g. of VI was dehydrated over potassium hydrogen sulfate. The unsaturated ester, of which 16 g. (91%) was obtained, boiled at 107° (2 mm.).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 75.1; H, 6.5.

p-Vinylphenylacetic acid (V). A mixture of 39 g. of the foregoing ester, 17 g. of potassium hydroxide in 100 ml. of anhydrous ethanol, and 0.2 g. of copper powder was kept at room temperature for 24 hr. The alcohol was distilled *in vacuo* and the residue acidified with cold dilute sulfuric acid. Successive recrystallization from aqueous ethanol and petroleum ether gave 30 g. (92%) of the desired acid, which melted at 101°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.1; H, 6.2. Found: C 74.1; H, 6.1.

Ethyl α-(p-vinylphenylacetyl)acetoacetate (IX). In the manner described for the synthesis of VIII, the chloride of (II) was prepared from 20 g. of potassium *p*-vinylphenylacetate and 15 g. of oxalyl chloride in 100 ml. of benzene and the solution added to the magnesium enolate of 13 g. of ethyl acetoacetate. After 12 hr. at room temperature, the product was worked up. Two distillations gave the pure ester IX, b.p. 144° (0.4 mm.) in a yield of 9 g. (30%); the residue was polymeric.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 69.9; H, 6.8.

An attempt to prepare the copper chelate from the crude product gave a dark green solution which, however, polymerized almost instantaneously. Also in the condensation of methyl *p*-vinylphenylacetate and acetone, in the presence of sodium hydride, most of the ester that reacted was converted into a polymer, and only a very small fraction boiling at 143–149° (1.5 mm.) was obtained, which gave the ferric chloride reaction expected of (*p*-vinylphenylacetyl)-acetone.

p-Bromophenylacetic acid, purified by sublimation and then melting at 114°, was prepared from *p*-bromoacetophenone[9] by the method of Schwenk and Bloch[10]; the yield was 20%, when the time of the hydrolysis of the thiomorpholide was extended to 25 hr.

Ethyl p-Bromophenylacetate was prepared as usual and boiled at 152° (22 mm.).

Methyl p-Bromobenzoate was obtained from the acid by the method of Clinton and Laskowski[6] in 92% yield (after recrystallization from ligroin it melted at 79–80°), and *p-bromophenyl-methyl-carbinol* according to Ziegler and Tiemann.[11] None of these substances exchanged the bromine atom for lithium, when treated with lithium metal or butyl lithium in ethereal solution.

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(9) R. Adams and C. R. Noller, *Org. Syntheses,* **Coll. Vol. I,** 109 (1941).

(10) E. Schwenk and E. Bloch, *J. Am. Chem. Soc.,* **64,** 3051 (1942).

(11) K. Ziegler and P. Tiemann, *Ber.,* **55,** 3406 (1922).

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

Friedel-Crafts Acylations of 1-Phenyl-2,5-dimethylpyrrole and 1,2-Diphenyl-5-methylpyrrole

RICHARD RIPS AND N. P. BUU-HOÏ

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Friedel-Crafts acylations of 1-phenyl-2,5-dimethylpyrrole yield diketones when acetyl and propionyl chloride are used, and both mono- and di-ketones with benzoyl and anisoyl chloride. On the other hand, 1,2-diphenyl-5-methylpyrrole gives predominantly monoketones with both types of acid chlorides, substitution occurring at the 4-position. Condensation of 3,4-diacylpyrroles with hydrazine hydrate leads to derivatives of 5,6-diazaisoindole, a new heterocyclic nucleus analogous to purine.

Although the pharmacological potentialities of the pyrrole nucleus have not yet been thoroughly investigated, several compounds in this series have already shown promising activity as possible antispasmodics and sedatives.[1] For further work in this field, pyrrole ketones represent convenient intermediates, and Friedel-Crafts acylations of some 1,2,5-trisubstituted pyrroles have therefore been investigated. 1-Phenyl-2,5-dimethylpyrrole (I) and 1,2-diphenyl-5-methylpyrrole (II), readily prepared by Knorr-Paal condensation of aniline with

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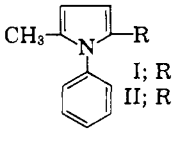
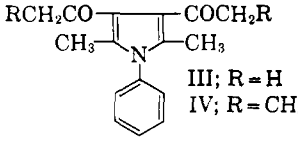
(1) *Cf.* N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.,* in press; E. Cionga, *Compt. rend.,* **200,** 780 (1935).

hexane-2,5-dione and phenacylacetone, respectively,[2] were chosen for the present study.

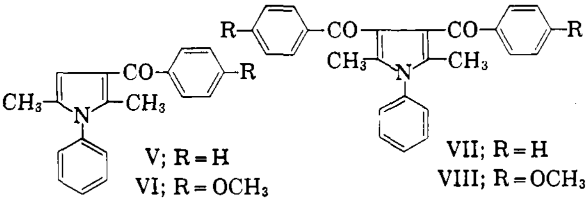
1-Phenyl-2,5-dimethylpyrrole underwent stannic chloride–catalyzed acylation with acetyl and propionyl chloride to give good yields of 3,4-diacetyl- (III) and 3,4-dipropionyl-1-phenyl-2,5-dimethylpyrrole (IV). Aluminum chloride has also been found useful as a catalyst, although the yields of diketones recorded were substantially lower; a study of the effect of temperature on the yields showed the optimum temperature of the reaction to be about 50° for stannic chloride and about 40° for aluminum chloride. When aromatic acid chlorides such as benzoyl and anisoyl chloride were used, both the monoketones (V and VI) and the diketones (VII and VIII) expected were obtained in practically equal amounts.



I; R = CH_3
II; R = C_6H_5



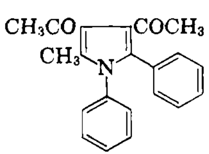
III; R = H
IV; R = CH_3



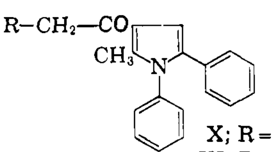
V; R = H
VI; R = OCH_3

VII; R = H
VIII; R = OCH_3

The ready diacetylation and dipropionylation of 1-phenyl-2,5-dimethylpyrrole is in sharp contrast with the behavior of 1,2-diphenyl-5-methylpyrrole. This latter gave with acetyl chloride predominantly a monoketone, with very little of the expected diketone (IX); with propionyl chloride, only a monoketone could be isolated. The monoacetylation product was shown to be 4-acetyl-1,2-diphenyl-5-methylpyrrole (X), as it was identical with the compound previously synthesized by Aggarwal, Qureshi, and Ray[3] by means of a Knorr-Paal condensation of aniline with 1,1-diacetyl-2-benzoylethane; by analogy, the monopropionylation product is assumed to possess formula XI.

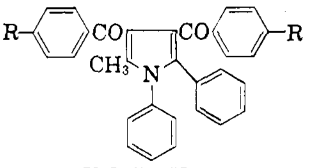


IX

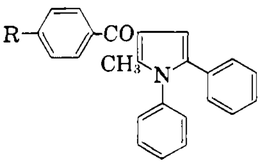


X; R = H
XI; R = CH_3

The fact that the 4-position in the molecule of 1,2-diphenyl-5-methylpyrrole is attacked preferentially to the 3-position is remarkable in view of the strong *ortho*-activation in the analogous molecule of biphenyl.[4] This anomaly cannot be accounted for entirely by the steric hindrance exerted at the 3-position by the phenyl radical, as benzoylation and anisoylation of II resulted in considerable amounts of the diketones XII and XIII along with the corresponding monosubstitution products XIV and XV.

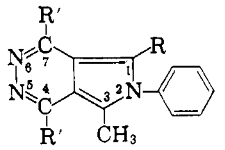


XII; R = H
XIII; R = OCH_3



XIV; R = H
XV; R = OCH_3

All the diketones reported above readily underwent condensation with hydrazine hydrate to give cyclic azines of general formula XVI, which are derivatives of 5,6-diazaisoindole, a new nitrogen heterocycle analogous to purine. This reaction not only proves the structure of the diketones used, but also provides a convenient route to compounds of biological interest as potential antipurines. An alternative method already reported[5] for the preparation of pyrrole diketones of type III is the Knorr-Paal condensation of primary amines with *sym*-tetraacetylenethane.



XVI

EXPERIMENTAL

Acetylation of 1-phenyl-2,5-dimethylpyrrole. (a) *With aluminum chloride.* To a water cooled solution of 15 g. of pyrrole I and 14 g. of finely powdered aluminum chloride in 200 ml. of dry carbon disulfide, 7.5 g. of acetyl chloride was added in small portions with stirring, and the mixture heated at 40° for 2 hr. on a warm water bath. After cooling, water was added, the organic layer washed with 5% aqueous sodium hydroxide, then with water, and dried over sodium sulfate, the solvent was distilled off, and the residue vacuum-fractionated. Yield: 9 g. (40%) of *3,4-diacetyl-1-phenyl-2,5-dimethylpyrrole,* b.p. 235–240°/15 mm., which crystallized from methanol in colorless prisms, m.p. 98°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5; O, 12.5. Found: C, 75.1; H, 6.8; N, 5.6; O, 12.8.

In an experiment in which aluminum chloride was added at 0° and the reaction mixture then kept overnight at 15°, an 18% yield of the same compound was recorded.

(b) *With stannic chloride.* To a solution of 20 g. of pyrrole I and 10 g. of acetyl chloride in 100 ml. of dry thiophene-free benzene, 36.5 g. of stannic chloride was added in small portions with stirring, and the mixture was then heated for 2 hr. at 50° on a water bath. After the usual treatment, 16 g. (52% yield) of diketone III was obtained.

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(2) L. Knorr, *Ann.*, **236**, 313 (1886); C. Paal, *Ber.*, **18**, 2254 (1885).

(3) J. S. Aggarwal, A. V. Qureshi, and J. N. Ray, *J. Am. Chem. Soc.*, **54**, 3988 (1932).

(4) *Cf.* N. P. Buu-Hoï, C. A. Coulson, P. Daudel, R. Daudel, M. Martin, A. Pullman, and B. Pullman, *Rev. sci.*, **85**, 1041 (1947).

(5) M. Dennstedt and J. Zimmerman, *Ber.*, **20**, 1760 (1887); D. B. Bright, *J. Am. Chem. Soc.*, **79**, 3202 (1957).

1,3,4,7-Tetramethyl-2-phenyl-5,6-diazaisoindole (XVI; R = R′ = CH_3). To a solution of 2.5 g. of the foregoing diketone in 10 ml. of ethanol, 1 g. of 95% hydrazine hydrate was added. An immediate exothermic reaction set up, with formation of a precipitate, which was collected and recrystallized twice from methanol. Yield: 2.2 g. (87.6%) of colorless needles, m.p. 318°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.5; H, 6.8; N, 16.7. Found: C, 76.2; H, 7.1; N, 16.8.

Propionylation of 1-phenyl-2,5-dimethylpyrrole. A solution of 10 g. of this pyrrole and 12 g. of propionyl chloride in 100 ml. of benzene was treated with 18.2 g. of stannic chloride, and the mixture treated in the same manner as for the preparation of ketone III. The yield was 14 g. (84%) of a diketone, b.p. 252°/20 mm., crystallizing from aqueous methanol in silky colorless needles, m.p. 66°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5; O, 11.3. Found: C, 76.2; H, 7.4; O, 11.2.

The same product was obtained in 23% yield when aluminum chloride was used as catalyst, the reaction being performed at room temperature and in carbon disulfide.

1,3-Dimethyl-2-phenyl-4,7-diethyl-5,6-diazaisoindole (XVI; R = CH_3, R′ = C_2H_5). Prepared from 1.4 g. of the foregoing diketone and 0.5 g. of hydrazine hydrate in 5 ml. of ethanol (3 hr. refluxing), this compound crystallized from aqueous methanol in silky colorless needles, m.p. 190°.

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.5; H, 7.6. Found: C, 77.2; H, 7.6.

Benzoylation of 1-phenyl-2,5-dimethylpyrrole. The reaction, performed in the usual way with 20 g. of this pyrrole, 18 g. of benzoyl chloride, and 37 g. of stannic chloride in benzene, yielded on vacuum-fractionation, two ketonic portions. The lower boiling portion (15 g., b.p. 260°/15 mm.) consisted of *3-benzoyl-1-phenyl-2,5-dimethylpyrrole* (V), crystallizing from methanol in colorless leaflets, m.p. 126°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.9; H, 6.2; N, 5.8. Found: C, 82.6; H, 6.5; N, 5.5.

The higher boiling fraction (10 g., b.p. 320–330°/17 mm.) consisted of *3,4-dibenzoyl-1-phenyl-2,5-dimethylpyrrole* (VII), crystallizing from ethanol in colorless plates, m.p. 186°.

Anal. Calcd. for $C_{26}H_{21}NO_2$: C, 82.9; H, 5.6; O, 8.4. Found: C, 82.6; H, 5.6; O, 8.5.

A similar reaction, using the same quantities of starting materials, and performed with aluminum chloride at 40° in carbon disulfide, gave 17 g. of the diketone (VII).

1,3-Dimethyl-1,4,7-triphenyl-5,6-diazaisoindole (XVI; R = CH_3, R′ = C_6H_5). Prepared by refluxing for 5 hr. a solution of 0.5 g. of diketone VII and 0.4 g. of hydrazine hydrate in 5 ml. of ethanol, this compound (0.4 g.) crystallized from ethanol in shiny pale yellow needles, m.p. 294°.

Anal. Calcd. for $C_{26}H_{21}N_3$: N, 11.2. Found: N, 11.0.

Anisoylation of 1-phenyl-2,5-dimethylpyrrole. The reaction-product from 20 g. of this pyrrole, 22 g. of anisoyl chloride, and 16.5 g. of aluminum chloride in carbon disulfide at 40°, likewise yielded two portions on vacuum-fractionation. The portion boiling at 275–290°/14 mm. (5.5 g.) crystallized from methanol to give *3-anisoyl-1-phenyl-2,5-dimethylpyrrole* (VI), lustrous colorless leaflets, m.p. 116°.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.6; H, 6.3; O, 10.5. Found: C, 78.3; H, 6.3; O, 10.8.

The portion b.p. *circa* 300°/2 mm. (15 g.) consisted of *3,4-dianisoyl-1-phenyl-2,5-dimethylpyrrole* (VIII), crystallizing from methanol in colorless leaflets, m.p. 183°.

Anal. Calcd. for $C_{28}H_{25}NO_4$: C, 76.5; H, 5.7; O, 14.6. Found: C, 76.4; H, 5.8; O, 14.7.

A stannic chloride–catalyzed acylation, using the same amounts of starting materials, and performed at 50°, yielded 10 g. of the monoketone and 10 g. of the diketone.

1,3-Dimethyl-1-phenyl-4,7-di(p-methoxyphenyl)-5,6-diazaisoindole (XVI; R = CH_3, R′ = C_6H_4—OCH_3). Crystallized from ethanol as lemon yellow plates, m.p. 295°.

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: N, 9.7. Found: N, 9.8.

Acetylation of 1,2-diphenyl-5-methylpyrrole. All the acylations of pyrrole II were effected with equimolar amounts of the pyrrole and of the acid chlorides. The acetylation, performed at various temperatures and with aluminum chloride as well as stannic chloride, always yielded predominantly *4-acetyl-1,2-diphenyl-5-methylpyrrole* (X), b.p. 240–242°/11 mm., crystallizing from methanol in fine colorless needles, m.p. 101–102°; the literature[3] gave m.p. 101°. The corresponding *oxime* crystallized from ethanol in colorless prisms, m.p. 176°.

Anal. Calcd. for $C_{19}H_{18}N_2O$: N, 9.7. Found: N, 9.7.

Repeated fractional crystallization from methanol of the higher boiling fractions yielded small amounts (less than 10% of the weight of the monoketone obtained) of *3,4-diacetyl-1,2-diphenyl-5-methylpyrrole* (IX), fine colorless needles, m.p. 161°, giving a yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.5; H, 6.0; N, 4.4; O, 10.1. Found: C, 79.4; H, 6.2; N, 4.7; O, 10.1.

The yields of monoketone plus diketone recorded were as follows:

Catalyst	Temperature, °C.	Yield, %
$AlCl_3$	0–5	15
$AlCl_3$	18	38
$AlCl_3$	40	52
$SnCl_4$	18	48
$SnCl_4$	60	59

1,2-Diphenyl-3,4,7-trimethyl-5,6-diazaisoindole (XVI; R = C_6H_5, R′ = CH_3). Crystallized from aqueous ethanol in silky colorless needles, m.p. 239°.

Anal. Calcd. for $C_{21}H_{19}N_3$: N, 13.4. Found: N, 13.3.

Propionylation of 1,2-diphenyl-5-methylpyrrole. With stannic chloride at 50° (3 hr. heating), a 60% yield of *4-propionyl-1,2-diphenyl-5-methylpyrrole,* b.p. 254–255°/15 mm., was obtained; recrystallization from ethanol gave lustrous colorless leaflets, m.p. 126°. No diketone could be isolated from the higher boiling portions.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.0; H, 6.6. Found: C, 82.9; H, 6.5.

With aluminum chloride as catalyst at 40°, the same monoketone was obtained in 40% yield.

The corresponding *semicarbazone* crystallized from ethanol in lustrous colorless leaflets, m.p. 260°.

Anal. Calcd. for $C_{21}H_{22}N_4O$: N, 16.2. Found: N, 16.2.

Benzoylation of 1,2-diphenyl-5-methylpyrrole. With stannic chloride at 50° as catalyst as above, two products were obtained. (a) A 49% yield of *4-benzoyl-1,2-diphenyl-5-methylpyrrole* (XIV), b.p. 244°/0.3 mm., crystallizing from methanol in colorless prisms, m.p. 131–132°.

Anal. Calcd. for $C_{24}H_{19}NO$: C, 85.4; H, 5.7. Found: C, 85.3; H, 5.7.

The corresponding *2,4-dinitrophenylhydrazone* crystallized from aqueous dioxane in fine violet-brown prisms, m.p. 190°.

Anal. Calcd. for $C_{30}H_{23}N_5O_4$: N, 13.5. Found: N, 13.4.

(b) A 32% yield of *3,4-dibenzoyl-1,2-diphenyl-5-methylpyrrole* (XII), b.p. >260°/0.5 mm., crystallizing from ethanol in fine colorless prisms, m.p. 200°.

Anal. Calcd. for $C_{31}H_{23}NO_2$: C, 84.3; H, 5.3. Found: C, 84.2; H, 5.2.

With aluminum chloride at 40°, a 39% yield of diketone XII was recorded.

1,2,4,7-Tetraphenyl-3-methyl-5,6-diazaisoindole (XVI; R = R′ = C_6H_5). Crystallized from ethanol in lemon yellow plates, m.p. 277°, giving a golden-yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{31}H_{23}N_3$: N, 9.6. Found: N, 9.5.

Anisoylation of 1,2-diphenyl-5-methylpyrrole. With stannic chloride at 50°, two products were also obtained in this case.

(a) A 51% yield of a portion b.p. 310–312°/11 mm., consisting of *4-anisoyl-1,2-diphenyl-5-methylpyrrole* (XV), crystallizing from ethanol in fine colorless prisms, m.p. 179–180°.

Anal. Calcd. for $C_{25}H_{21}NO_2$: C, 81.7; H, 5.8. Found: C, 81.4; H, 5.7.

The corresponding *semicarbazone* crystallized from ethanol in colorless needles, m.p. 241°.

Anal. Calcd. for $C_{26}H_{24}N_4O_2$: N, 13.2. Found: N, 13.5.

(b) A 40% yield of *3,4-dianisoyl-1,2-diphenyl-5-methylpyrrole* (XIII), b.p. 300–305°/0.5 mm., crystallizing from ethanol in colorless prisms, m.p. 208°.

Anal. Calcd. for $C_{33}H_{27}NO_4$: C, 79.0; H, 5.4; N, 2.8. Found: C, 78.7; H, 5.4; N, 2.8.

With aluminum chloride, a 29% yield of diketone XIII was obtained at 40°, and a 9% yield when the reaction was performed at room temperature.

1,2-Diphenyl-3-methyl-4,7-di(p-methoxyphenyl)-5,6-diazaisoindole (XVI; R = C_6H_5, R′ = C_6H_5—OCH_3). Crystallized from ethanol in yellow plates, m.p. 301°, giving a deep yellow coloration with sulfuric acid.

Anal. Calcd. for $C_{33}H_{27}N_3O_2$: C, 79.7; H, 5.5; N, 8.7. Found: C, 79.7; H, 5.5; N, 8.7.

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