9H-Pyrrolo[1,2-*a*]indoles[1]

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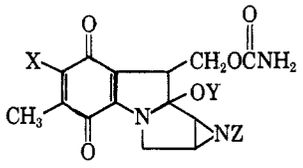
The important mitomycin antibiotics have the aziridinopyrrolo[1,2-*a*]indolequinone structure (**1**).[3] An approach to the synthesis of compounds of this structure was envisioned with 9H-pyrrolo[1,2-*a*]indole (**2**) as a base from which further explorations would begin. The related 9-ketone (**3**) was first isolated by Shirley[4] as a minor product from the carbonation of lithiated



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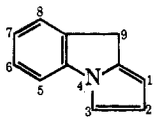

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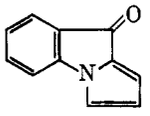
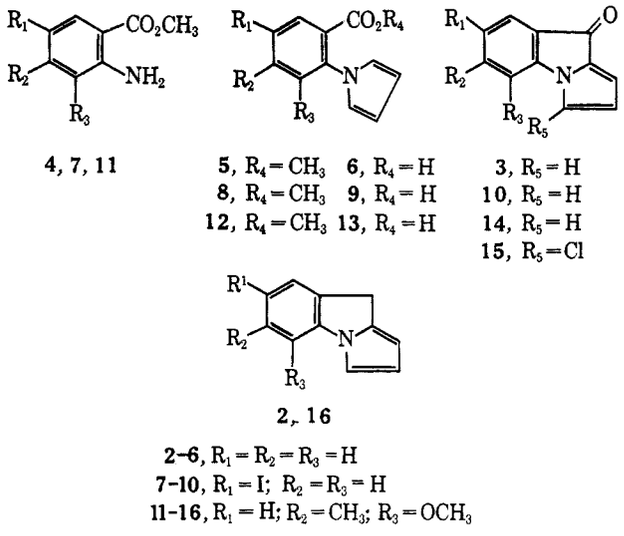


3

1-phenylpyrrole. Huisgen[5] prepared the ketone **3** by decarboxylation of a keto acid obtained from the Friedel–Crafts cyclization of 1-phenyl-2-carboxy-3-cyanopyrrole. Wolf–Kishner reduction of the semicarbazone of **3** afforded the parent heterocycle **2**.[6] Josey[7] obtained ketone **3** in 23% over-all yield from methyl anthranilate (**4**) as outlined in Chart I. The pyrrole ester (**5**) was prepared by condensation of amino ester **4** with 2,5-dimethoxytetrahydrofuran in glacial acetic acid. This reaction is a very general one for preparing N-substituted pyrroles.[8] Saponification of pyrrole ester **5** was accomplished with potassium hydroxide in ethylene glycol. Cyclization of the resulting acid (**6**) with polyphosphoric acid afforded ketone **3** in 32% yield. In our work, based on the Josey–Jenner approach,[7] we have prepared ketone **3** and heterocycle **2** and extended the procedures to the preparation of 7-iodo ketone (**10**), 5-methoxy-6-methyl ketone (**14**), the related heterocycle (**16**), and the 3-chloro-5-methoxy-6-methyl ketone (**15**). Our modifications consisted of conducting the saponification of the esters **5**, **8**, and **12** with aqueous methanolic potassium hydroxide and, most importantly, performing the Friedel–Crafts cyclizations on the acid chlorides (derived from the acids **6**, **9**, and **13** by treating them with phosphorus pentachloride) with stannic chloride as a catalyst.[9] Thus, ketone **3** was obtained in 50% over-all yield (based on average yields for each step, or, 57% based on best yields) from **4** with the cyclization proceeding in 74% average (but as high as 87%) conversion. The iodo ketone **10** was obtained in 28% yield from methyl 5-iodoanthranilate **7**[10] without purification of unstable iodo ester **8** and acid **9**. These intermediates were purified for analysis with great reduction in yield. Methoxymethyl ketone **14** was obtained in 44% yield based on amino ester **11** while chloro ketone **15** was inadvertently prepared in 27% over-all yield by the action of excess phosphorus pentachloride (and subsequent stannic chloride) in the conversion of acid **13** into its acid chloride. Ester **11** was obtained by esterification and reduction of the known 3-methoxy-4-methyl-2-nitrobenzoic acid.[11] Wolf–Kishner reduction of the semicarbazones of ketones **3** and **14** afforded the respective heterocycles **2** and **16** in 88 and 72% yields.

CHART I



4, 7, 11

5, $R_4 = CH_3$ **6**, $R_4 = H$
8, $R_4 = CH_3$ **9**, $R_4 = H$
12, $R_4 = CH_3$ **13**, $R_4 = H$

3, $R_5 = H$
10, $R_5 = H$
14, $R_5 = H$
15, $R_5 = Cl$

2, 16

2–6, $R_1 = R_2 = R_3 = H$
7–10, $R_1 = I$; $R_2 = R_3 = H$
11–16, $R_1 = H$; $R_2 = CH_3$; $R_3 = OCH_3$

The nmr data for all the pyrroles studied are assembled in Table I. The coupling constants for the pyrrole protons correspond well with those cited in a recent review.[12] In the cyclized compounds **2**, **3**, **10**, **14**, and **16** where the C_3 protons are fixed in the planes of the benzene rings, there is a marked deshielding of their signals. In the methoxymethyl compounds **12**, **13**, **14**, **15**, and **16**, the peak height of the C methyl was reduced and the line was broadened (relative to O methyl) indicating coupling to the adjacent aromatic proton. A reciprocal line broadening was observed in the signal of the ring proton (C_7) in each compound. The variation of methoxyl resonance for amino ester **11** (δ 3.69) to the pyrrole ester **12** (δ 3.19) and acid **13** (δ 3.25) to the cyclized products **14** (δ 3.85), **15** (δ 3.80), and **16** (δ 3.82) is a record of the methoxyl group

(1) This research was supported by National Institutes of Health Grant GM 12758.

(2) National Science Foundation Undergraduate Research Participant, 1965.

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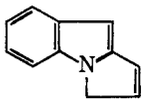
(5) R. Huisgen and E. Laschtuvka, *Chem. Ber.*, **93**, 81 (1960).

(6) 9H-Pyrrolo[1,2-*a*]indole (**2**)[a] and its 7-benzyloxy derivative[b] have been obtained in independent attempts to synthesize the 3H-pyrrolo[1,2-*a*]indole system (i): (a) E. E. Schweizer and K. K. Light, *J. Org. Chem.*, **31**, 870,



i

2912 (1966). (b) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **30**, 2904 (1965). (c) A 1-chloro-3-methoxalyl derivative of **2** has been obtained in a novel rearrangement reaction: W. A. Remers, *J. Am. Chem. Soc.*, **86**, 4608 (1964).

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(8) N. Clauson-Haas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952).

(9) W. S. Johnson, *Org. Reactions*, **2**, 114 (1944).

(10) P. H. Petyunin and M. E. Konshin, *J. Gen. Chem. USSR*, **27**, 541 (1957).

(11) J. Simonsen and M. G. Rau, *J. Chem. Soc.*, 1342 (1921).

(12) A. R. Katritzky, Ed., "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, p 131.

TABLE I

NMR DATA FOR PYRROLES PREPARED[a]

No.	Solvent	Benzene	Pyrrole	Other
2	CCl_4	7.06–7.41 (m)	6.99 (dd, J_{13} = 1.4 cps, J_{23} = 2.8 cps, C_3) 6.26 (dd, J_{12} = 3.0 cps, J_{23} = 2.8 cps, C_2) 6.02 (dd, J_{12} = 3.0 cps, J_{13} = 1.4 cps, C_1)	3.97 (s, C_9)
3	CCl_4	7.1–7.6 (m)	7.02 (dd, J_{23} = 2.5 cps, J_{13} = 1.0 cps, C_3) 6.68 (dd, J_{12} = 3.8 cps, J_{12} = 1.0 cps, C_1) 6.25 (dd, J_{12} = 3.8 cps, J_{23} = 2.5 cps, C_2)	
5	CCl_4	7.3–7.8 (m)	6.70 (t, J = 2.4 cps, α) 6.17 (t, J = 2.4 cps, β)	3.58 (s, $COCH_3$)
6	CCl_4	7.2–7.9 (m)	6.67 (t, J = 2.4 cps, α) 6.15 (t, J = 2.4 cps, β)	8.57 (s, COOH)
8	CS_2	7.93 (d, J_{35} = 2.0 cps, C_3) 7.75 (dd, J_{56} = 8.1 cps, J_{35} = 2.0 cps, C_5) 6.97 (d, J_{56} = 8.1 cps, C_6)	6.57 (t, J = 2.2 cps, α) 6.10 (t, J = 2.2 cps, β)	3.57 (s, $COCH_3$)
9	CS_2	8.17 (d, J_{35} = 2.0 cps, C_3) 7.83 (dd, J_{56} = 8.3 cps, J_{35} = 2.0 cps, C_5) 7.00 (d, J_{56} = 8.3 cps, C_6)	6.62 (t, J = 2.2 cps, α) 6.13 (t, J = 2.2 cps, β)	11.7 (s, COOH)
10	DMSO	7.87 (dd, J_{56} = 8.1 cps, J_{68} = 1.6 cps, C_6) 7.70 (d, J_{68} = 1.6 cps, C_8) 7.30 (d, J_{56} = 8.1 cps, C_5)	7.62 (dd, J_{23} = 2.6 cps, J_{13} = 1.0 cps, C_3) 6.81 (dd, J_{12} = 3.6 cps, J_{13} = 1.0 cps, C_1) 6.33 (dd, J_{12} = 3.6 cps, J_{23} = 2.6 cps, C_2)	
12	CCl_4	7.28 (d, J_{56} = 8.0 cps, C_6) 7.12 (d, J_{56} = 8.0 cps, C_5)	6.67 (t, J = 2.2, α) 6.14 (t, J = 2.2 cps, β)	3.51 (s, $COCH_3$) 3.19 (s, OCH_3) 2.31 (s, CH_3)
13	$CDCl_3$	7.58 (d, J_{56} = 7.8 cps, C_6) 7.20 (d, J_{56} = 7.8 cps, C_5)	6.75 (t, J = 2.0 cps, α) 6.23 (t, J = 2.0 cps, β)	3.25 (s, OCH_3) 2.35 (s, CH_3) 10.54 (s, COOH)
14	CCl_4	7.15 (d, J_{78} = 7.5 cps, C_8) 6.78 (d, J_{78} = 7.5 cps, C_7)	7.14 (dd, J_{23} = 2.7 cps, J_{13} = 1.0 csp, C_3) 6.60 (dd, J_{12} = 3.7 cps, J_{13} = 1.0 cps, C_1) 6.17 (dd, J_{12} = 3.7 cps, J_{23} = 2.7 cps, C_2)	3.85 (s, OCH_3) 2.30 (s, CH_3)
15	CCl_4	7.21 (d, J_{78} = 7.2 cps, C_8) 6.97 (d, J_{78} = 7.2 cps, C_7)	6.68 (d, J_{12} = 3.8 cps, C_2) 6.12 (d, J_{12} = 3.8 cps, C_1)	3.80 (s, OCH_3) 2.37 (s, CH_3)
16	$CDCl_3$	7.02 (d, J_{78} = 7.4 cps, C_8) 6.80 (d, J_{78} = 7.4 cps, C_7)	7.30 (dd, J_{23} = 2.8 cps, J_{13} = 1.1 cps, C_3) 6.35 (dd, J_{12} = 3.5 cps, J_{23} = 2.8 cps, C_2) 6.08 (dd, J_{12} = 3.5 cps, J_{13} = 1.1 cps, C_1)	3.82 (s, OCH_3) 3.75 (s, CH_2) 2.33 (s, CH_3)

[a] The spectra were obtained with a Varian A-60 instrument, probe temperature 38°. The ordering of the data is signal reported relative to internal tetramethylsilane, δ = 0.00 ppm; s (singlet), d (doublet), t (triplet), dd (doubled doublet), m (multiplet) is peak multiplicity; J values are given in cycles per second; proton location. The spectra of **2** and its 7-benzyloxy derivative have been reported.[6]

location relative to the pyrrole ring. In the uncyclized compounds, the preferred rotamer must be one where the pyrrole plane is skewed relative to the benzene plane; thus the methoxyl can be above the pyrrole plane and can be anisotropically shielded. In the cyclized products, the pyrrole and benzene rings are coplanar and the methoxyl can no longer be affected by the pyrrole shielding region.

Experimental Section[13]

1-(2-Methoxycarbonylphenyl)pyrrole (5).[7]—Condensation of 151.2 g (1.0 mole) of methyl anthranilate (Aldrich) with 132.2 g (1.0 mole) of 2,5-dimethoxytetrahydrofuran (Aldrich) in 200 ml of glacial acetic acid for 1.5 hr followed by direct distillation of the reaction mixture afforded 161.1 g (80%) of pyrrole ester **5**: bp 83–85° (0.15 mm) [lit.[7] bp 110° (3 mm)]; λ_{max}^{EtOH} 213 mμ (ϵ 15,100), 248 (6450), 287 (1660); λ_{max}^{film} 5.80, 6.22, 6.66, 7.49, 7.70, 8.82, 10.74, 13.01, 13.68 μ. Yields up to 80% have been obtained depending on the efficiency of the distillation.

1-(2-Carboxyphenyl)pyrrole (6).[7]—A solution of 69.1 g (0.34 mole) of ester **5** in a reagent prepared from 97 g of potassium hydroxide dissolved in 400 ml of 50% aqueous methanol was refluxed for 2 hr. Acidification and subsequent work-up of the reaction mixture afforded the acid **6** which was crystallized once from ether–hexane to give 58.3 g of product: mp 100–103° (lit.[7] mp 106–107°); 91% yield; $\lambda_{max}^{CHCl_3}$ 3.2–4.0, 5.87, 6.32, 6.78, 7.59, 7.80, 9.37 μ.

9-Keto-9H-pyrrolo[1,2-*a*]indole (3).—A solution of 60 g (0.32 mole) of the acid **6** in 1200 ml of benzene was converted into its acid chloride by treatment with 70.2 g (0.34 mole) of phosphorus pentachloride for 1 hr. Addition of 175.2 g (0.67 mole) of stannic chloride was followed by stirring for 0.75 hr. A hydrolytic work-up consisting of stirring the reaction mixture with ice–hydrochloric acid for 1 hr was followed by removal of tin salts and extraction of the aqueous layers by chloroform. The crude organic fraction (solvent free) upon short-path distillation [bp 143–146° (0.28 mm)] afforded 47.0 g (87%), of ketone **3**: mp 119.5–121.5° (lit.[7] mp 121–122°); λ_{max}^{EtOH} 214 mμ (ϵ 9130), 242 (s) (23,200), 250 (27,400), 274 (9890), 282 (7910), 286 (s) (6080), 327 (7690); $\lambda_{max}^{CHCl_3}$ 5.90, 6.18, 6.80, 7.65, 9.26, 11.01, 11.42 μ. Longer cyclization or hydrolysis periods decreased yields.

9H-Pyrrolo[1,2-*a*]indole (2).—Using Huisgen's[5] procedures, 13.30 g (0.078 mole) of ketone **3** was converted into its semicarbazone (90% yield) mp 210–212° (lit.[5] mp 212–214°). A mixture of 16.00 g (0.071 mole) of the semicarbazone, 12.00 g (0.21 mole) of potassium hydroxide, and 72 ml of diethylene glycol was heated at 145–155° until gas evolution ceased. The mixture was cooled, acidified with hydrochloric acid, and continuously extracted with hexane for 12 hr. The hexane solution was

(13) Melting points were determined on a Fisher-Johns apparatus and are corrected. Infrared spectra were obtained with a Perkin-Elmer Infracord. Ultraviolet spectra were determined using a Cary 15 spectrophotometer. A nitrogen atmosphere was maintained over all reactions by using the apparatus described by Johnson and Schneider.[14] Analyses were done by Spang Microanalytical Laboratory.

(14) W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1950).

washed with sodium carbonate, washed with water, and dried with sodium sulfate. Removal of the solvent afforded a crude product which was sublimed at 60–65° (0.20 mm) yielding 9.69 g of the hydrocarbon **2** (88% yield), mp 87.5–90.0°. One recrystallization from absolute ethanol afforded pure hydrocarbon: mp 90–91° (lit.[5] mp 89.5–91°); 74% yield; $\lambda_{max}^{CCl_4}$ 3.22, 3.25, 3.28, 3.43, 6.14 μ; λ_{max}^{EtOH} 262 mμ (ϵ 15,300), 292 (2200).

1-(4-Iodo-2-methoxycarbonylphenyl)pyrrole (8). A.—Following the procedure for ester **5**, 10.00 g (0.036 mole) of methyl 5-iodoanthranilate[10] was treated with 4.80 g (0.036 mole) of 2,5-dimethoxytetrahydrofuran in 50 ml of glacial acetic acid. After removal of solvents at reduced pressure, the crude residue was saponified as described below.

B.—The 2,5-dimethoxytetrahydrofuran (2.4 g, 0.018 mole) was added to a solution of 5.0 g (0.018 mole) of methyl 5-iodoanthranilate in 40 ml of toluene containing a trace of *p*-toluenesulfonic acid. After refluxing for 4 hr under a water separator, the toluene was distilled off at reduced pressure (water pump) and the dark residue was vacuum distilled. Material boiling at 141–149° (0.52 mm) was collected. The impure pyrrole (the infrared spectrum showed the presence of traces of amine), amounting to 4.20 g (71%) was chromatographed on silica gel (Davison) with 50% chloroform in carbon tetrachloride as eluent. The fractions free of the amine crystallized from chloroform–hexane solution to give 1.02 g (17%) of crystals, mp 75–77°. Several recrystallizations gave pure **8** as colorless crystals: mp 78–79°; λ_{max}^{EtOH} 263 mμ (ϵ 9440); $\lambda_{max}^{CCl_4}$ 5.79, 6.70, 6.96, 7.50, 7.76, 7.90, 8.87, 9.16 μ.

Anal. Calcd for $C_{12}H_{10}INO_2$: C, 44.1; H, 3.1; I, 38.8; N, 4.3. Found: C, 44.11; H, 2.9; I, 38.7; N, 4.31.

1-(4-Iodo-2-carboxyphenyl)pyrrole (9). A.—A solution of 7.90 g (0.024 mole) of crude ester **8** (from A above) was treated with aqueous alcoholic potassium hydroxide as in the unsubstituted case. After work-up, 6.85 g (90%) of crude 1-(4-iodo-2-carboxyphenyl)pyrrole (**9**) was obtained as a violet solid, mp 100–110°. The material tarred readily and could not be further purified. It was used directly in the cyclization step as described below.

B.—The once-recrystallized (procedure B above) 1-(4-iodo-2-methoxycarbonylphenyl)pyrrole (**8**, 0.45 g, 1.4 mmoles) was refluxed with 0.39 g (7.0 mmoles) of potassium hydroxide in 20 ml of 50% aqueous methanol for 1 hr under nitrogen. The solution was then diluted with 30 ml of water, extracted once with ether, and poured into cold, dilute hydrochloric acid. Work-up afforded 0.40 g (93%) of 1-(4-iodo-2-carboxyphenyl)pyrrole as a pink solid: mp 127–128°; λ_{max}^{EtOH} 261 mμ (ϵ 15,700); $\lambda_{max}^{CHCl_3}$ 3.3–4.0, 5.88, 6.36, 6.77, 7.58, 9.20 μ.

Anal. Calcd for $C_{11}H_8INO_2$: C, 42.21; H, 2.60; I, 40.5; N, 4.50. Found: C, 42.4; H, 2.8; I, 40.6; N, 4.51.

7-Iodo-9-keto-9H-pyrrolo[1,2-*a*]indole (10).—Phosphorus pentachloride (1.88 g, 9.00 mmoles) was added in portions to a cold, stirred solution of 2.09 g (6.68 mmoles) of the crude **9** (A above) in 50 ml of dry benzene under nitrogen. After the addition was complete, the temperature was allowed to rise to room temperature while the solution was stirred for 45 min. A solution of 3.48 g (13.4 mmoles) of anhydrous stannic chloride in 20 ml of dry benzene was then added over 30 min with cooling. The mixture was stirred for 12 hr. Work-up gave 0.899 g of the crude, brown ketone. This material was purified by chromatography on alumina (Woelm, activity II), using 25% chloroform in carbon tetrachloride as eluent, to give 0.846 g (42.9%) of 7-iodo ketone (**10**), mp 185–190°. Several recrystallizations from CCl_4 gave dull, yellow needles: mp 194–195°; λ_{max}^{EtOH} 228 mμ (ϵ 6790), 248 (s) (16,500), 253 (18,100), 277 (9000), 287 (9830), 345 (5160); $\lambda_{max}^{CCl_4}$ 5.88, 6.22, 6.79, 7.23, 7.50, 9.22 μ.

Anal. Calcd for $C_{11}H_6INO$: C, 44.8; H, 2.1; I, 43.0; N, 4.8. Found: C, 44.7; H, 2.0; I, 43.1; N, 4.7.

Methyl 3-Methoxy-4-methylanthranilate (11).—Methyl 2-nitro-3-methoxy-4-methylbenzoate (3.34 g 14.8 mmoles, mp 35–36° *from the known acid*[11]) in 100 ml of methanol over 200 mg of 10% palladium on charcoal rapidly took up 51 mmoles of hydrogen at an initial pressure of 41.5 psi. The mixture was filtered and the methanol was removed at reduced pressure until a white solid began separating from solution. A total of 2.51 g (84.1%) of material was collected in three crops, mp 85–88°. Several recrystallizations from methanol gave pure methyl 3-methoxy-4-methylanthranilate as colorless needles: mp 90–91°; λ_{max}^{EtOH} 224 mμ (ϵ 36,600), 251 (9070), 336 (5950); $\lambda_{max}^{CHCl_3}$ 2.86, 2.96, 3.41, 5.94, 6.18, 6.28, 6.91, 7.64, 8.98, 9.37, 9.86 μ.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.5; H, 6.8; N, 7.3.

1-(2-Methoxy-3-methyl-6-methoxycarbonylphenyl)pyrrole (12).—2,5-Dimethoxytetrahydrofuran (0.677 g, 5.13 mmoles) was added to a solution of 1.00 g (5.13 mmoles) of methyl 3-methoxy-4-methylanthranilate in 10 ml of glacial acetic acid. The solution, which turned dark on warming, was refluxed for 5 hr under nitrogen. The acetic acid was then distilled off at reduced pressure (water pump) and the residue was vacuum distilled to give 0.93 g (83%) of the 1-(2-methoxy-3-methyl-6-methoxycarbonylphenyl)pyrrole as a colorless liquid, bp 122.5–125° (0.75 mm).

A small sample was redistilled but the distilled material still failed to solidify even after prolonged chilling. Further, the nmr spectrum and vpc data indicated the presence of an impurity, although not the amine. The material had λ_{max}^{EtOH} 224 mμ (ϵ 22,400), 296 (2500); λ_{max}^{film} 3.42, 5.79, 6.24, 6.66, 7.69, 9.45, 12.51, 13.70 μ.

1-(2-Methoxy-3-methyl-6-carboxyphenyl)pyrrole (13).—Saponification was carried out by refluxing 0.50 g (2.04 mmoles) of 1-(2-methoxy-3-methyl-6-methoxycarbonylphenyl)pyrrole (**12**) with 0.57 g (10.2 mmoles) of potassium hydroxide in 10 ml of 50% aqueous methanol for 2 hr under nitrogen. On work-up the acid separated as a white solid (0.45 g, 94%), mp 160–164°. Recrystallization from chloroform–hexane gave pure 1-(2-methoxy-3-methyl-6-carboxyphenyl)pyrrole (**13**): mp 164–165°; λ_{max}^{EtOH} 224 mμ (ϵ 12,100), 288 (1270); $\lambda_{max}^{CHCl_3}$ 3.35, 3.4–4.0, 5.85, 6.25, 6.72, 7.85, 9.21, 9.77 μ.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.6; H, 5.6; N, 6.0.

5-Methoxy-6-methyl-9-keto-9H-pyrrolo[1,2-*a*]indole (14).—To a suspension of 11.30 g (48.9 mmoles) of pyrrole acid **13** in 200 ml of dry benzene, chilled in an ice bath under a nitrogen atmosphere, was added 10.20 g (48.9 mmoles) of phosphorus pentachloride. The dark solution was stirred for 0.5 hr. A solution of 26.50 g (102 mmoles) of stannic chloride was then added slowly with cooling and the resulting mixture was stirred for 6 hr. The mixture was hydrolyzed with ice–hydrochloric acid, the salts were filtered, and the organic phase was separated and worked up to afford 1.55 g of dark brown solid. This solid was combined with a crude pot residue (7.00 g) and sublimed [100° (0.20 mm)]. The sublimate was chromatographed on alumina (Woelm activity II, 25% $CHCl_3$ in CCl_4 as eluent) and the eluted material was crystallized from absolute ethanol to yield 5.55 g (53%) of ketone **14** as yellow needles: mp 126–127°; λ_{max}^{EtOH} 225 mμ (7310), 242 (15,500), 256 (29,900), 282 (s) (6110), 288 (7880), 295 (s) (7180), 334 (9050); $\lambda_{max}^{CCl_4}$ 3.40, 3.56, 5.86, 6.25, 6.80, 7.02, 7.34, 7.82, 8.50, 9.06, 9.50, 10.53, 11.53 μ.

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.2; H, 5.2; N, 6.6. Found: C, 73.1; H, 5.4; N, 6.5.

5-Methoxy-6-methyl-9H-pyrrolo[1,2-*a*]indole (16).—The semicarbazone of ketone **14** was prepared in 92% yield from 4.55 g (21.4 mmoles) as in the unsubstituted case. A mixture of 5.32 g (19.7 mmoles) of the semicarbazone, 2.24 g (40 mmoles) of potassium hydroxide, and 20 ml of diethylene glycol was held at 130° for 24 hr. Work-up by extraction with hexane followed by solvent removal gave a dark red oil which was distilled [bp 113–114° (0.37 mm)] to afford 2.81 g (72%) of a pale yellow liquid which solidified on cooling. A portion of this solid (mp ≈0°) was recrystallized three times from hexane to afford a pale yellow solid: mp 35–36°; $\lambda_{max}^{isooctane}$ 212 mμ (ϵ 32,400) 243 sh (8000), 265 (17,500), 295 sh (800); $\lambda_{max}^{CCl_4}$ 3.42, 6.15 μ.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 78.3; H, 6.6; N, 7.0.

3-Chloro-5-methoxy-6-methyl-9-keto-9H-pyrrolo[1,2-*a*]indole (15).—To a suspension of 1.00 g (4.33 mmoles) of 1-(2-methoxy-3-methyl-6-carboxyphenyl)pyrrole **13** in 30 ml of dry benzene, chilled in an ice bath under nitrogen, was added 1.20 g (5.77 mmoles) of phosphorus pentachloride slowly with stirring. The solution turned dark green and was stirred without cooling for 30 min. A solution of 2.24 g (8.60 mmoles) of anhydrous stannic chloride in 15 ml of dry benzene was then added slowly with cooling and the dark mixture was stirred for 72 hr at room temperature. Work-up gave a crude ketone which was purified by chromatography on alumina (Woelm, activity II) using 25% chloroform in carbon tetrachloride as eluent. The product was obtained as dull, yellow needles, mp 130–150° (0.359 g, 33.6%). Recrystallization from CCl_4 gave material whose nmr spectrum indicated the 3 proton to be missing, and which analyzed correctly for the 3-chloro-5-methoxy-6-methyl compound: mp 152–

154°; λ_{max}^{EtOH} 220 mμ (ε 4510), 243 (s) (17,400), 248 (20,300), 286 (s) (5580), 294 (7140), 301 (s) (6200), 349 (8160); $\lambda_{max}^{CCl_4}$ 3.43, 3.58, 5.89, 6.20, 6.78, 6.90, 7.15, 7.41, 7.80, 7.95, 9.51, 11.62, 12.05 μ.

Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.0; H, 4.1; N, 5.7. Found: C, 63.3; H, 4.2; N, 5.6.

A New Synthesis of 2,2-Dimethyl-3-isopropylidenecyclopropyl Propionate

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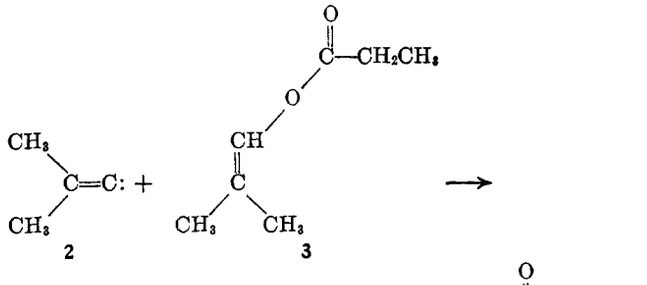
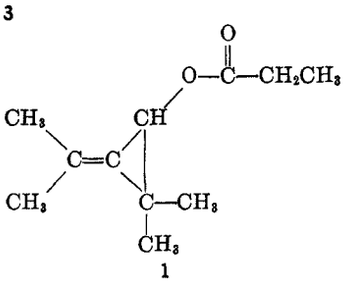
The title compound (**1**) was proposed as the sex attractant of the virgin female American cockroach, *Periplaneta americana* (L), by members of this laboratory.[1] Widespread interest in this compound was evidenced by reports of unsuccessful attempts to synthesize it,[2-4] but a successful synthesis by Day and Whiting[5] showed that **1** did not have biological activity. Our findings corroborate this.[6]

We wish to report a new synthesis of this compound. The general approach was to generate the vinylidenecarbene (**2**) or an entity behaving similarly which could than be made to react with the appropriate enol ester (**3**).



2 **3**

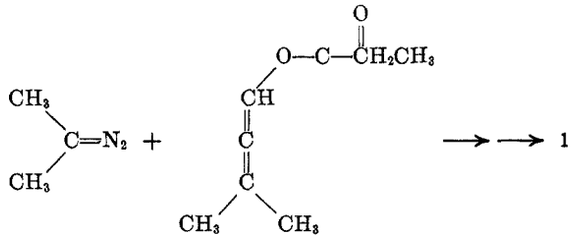


1

2-Methyl-1-propenyl propionate (**3**) was prepared from isobutyraldehyde, priopionic anhydride, and a catalytic amount of *p*-toluenesulfonic acid.

Tanabe and Walsh have reported that **2** could be generated from the reaction of either 1-chloro-2-methylpropene or 3-chloro-2-methylpropene with potassium *t*-butoxide in tetrahydrofuran.[7] When olefin **3** was used as the carbene acceptor, however, the reaction was unsuccessful.[8] The reaction of 1,1-dibromo-2-methylpropene with methyllithium in the presence of cyclohexene did form an isopropylidenecyclopropane.[9] As the latter method was obviously inapplicable when the olefin was an enol ester, a suitable modification was sought.

1,1-Dibromo-2-methylpropene reacted exothermically with magnesium in dry tetrahydrofuran in the presence of cyclohexene. Only a trace of the adduct, 7-isopropylidenenorcarane, was detected by gas chromatography. When enol ester **3** was used in place of cyclohexene, the desired product (**1**) was obtained in 18% yield. No other products were obtained in more than 1.5% yield and these were not studied further. It had identical glpc retention time and infrared and nmr spectra as the product obtained by Day and Whiting[5b,10] from different fragments, as shown, thus confirming the structure of **1**.



Thus far, attempts to extend the scope of this novel reaction have failed. No adducts were formed when ethyl vinyl ether, 1-cyclohexenyl acetate, or isopropenyl acetate were used. The reaction of 1,1-dibromo-2-methylpropene with enol ester **3** using zinc–copper couple[11] in tetrahydrofuran or 1,2-dimethoxyethane likewise failed.

The nature of the carbenoid species is unknown. When 1,1-dibromo-2-methylpropene was treated with magnesium in tetrahydrofuran and subsequently either **3** or Dry Ice was added neither **1** nor 2-bromo-3-methylcrotonic acid was formed. This would indicate that 1-bromo-2-methylpropenylmagnesium bromide, which is presumably the first intermediate, decomposes rapidly under the reaction conditions. However, this sheds no light on the actual species involved in the addition.

Experimental Section[12]

2-Methyl-1-propenyl Propionate (**3**).—A mixture of isobutyraldehyde (115 g, 1.6 moles), propionic anhydride (415 g, 3.2 moles), and *p*-toluenesulfonic acid monohydrate (3.8 g, 0.02 mole) was refluxed for 3 hr. After cooling, the mixture was poured into aqueous sodium carbonate, and additional sodium carbonate was added, keeping the temperature below 40° by the addition of ice, until carbon dioxide was no longer evolved. Two 250-ml portions of ether were used for extraction, after which the ether was washed with 50-ml portions of water and dried with magnesium sulfate. The solution was filtered and freed of solvent and the residue was distilled to give 100 g (55%) of 2-methyl-1-propenyl propionate, bp 145–147° (lit.[2] bp 140°).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.37; H, 9.62.

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(4) J. R. Chapman, *Tetrahedron Letters*, 113 (1966).

(5) (a) A. C. Day and M. C. Whiting, *Proc. Chem. Soc.*, 368 (1964); (b) A. C. Day and M. C. Whiting, *J. Chem. Soc.*, 464 (1966).

(6) M. Jacobson and M. Beroza, *Science*, **147**, 748 (1965).

(7) M. Tanabe and R. A. Walsh, *J. Am. Chem. Soc.*, **85**, 3522 (1963).

(8) Meinwald[2] has since described this reaction.

(9) H. D. Hartzler [*J. Am. Chem. Soc.*, **86**, 526 (1964)] has since described this reaction.

(10) We wish to thank Professor Day for carrying out this comparison.

(11) E. LeGoff, *J. Org. Chem.*, **29**, 2648 (1964).

(12) Boiling points are uncorrected. Analysis for compound **3** was performed by Galbraith Laboratories, Knoxville, Tenn., and for compound **1** by Chemco, Inc., Washington, D. C. Preparative chromatography was run on an Aerograph Autoprep with a 6.1 m × 9.5 mm column of SE-30 on Chromosorb W at 165°, retention time 10 min.