Facile Introduction of Ester Groups into the Pyrrole Nucleus *via* Trichloroacetylation and Alcoholysis[1]

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The trichloroacetylation of alkylpyrroles, α-ethoxycarbonylpyrroles, and dipyrrylmethanes is described, using trichloroacetyl chloride and appropriate bases as acid scavengers. Treatment of trichloroacetylpyrroles with alcohols and mild base converts them directly into pyrrole esters of primary alcohols; secondary and tertiary alcohols do not give synthetically useful yields. Trifluoroacetylpyrroles are not directly converted to esters.

Pyrrole esters are most generally prepared by ring synthesis, a method usually giving good yields but limited to certain substitution patterns and to esters which will survive the condensation conditions. Pyrrole acids are readily prepared *via* sulfuryl chloride oxidation of nuclear methyl groups; however, esterification with reagents other than diazomethane frequently proves troublesome.

Potentially, the most versatile method would be the direct introduction of the ester functionality into a preexisting pyrrole ring. Existing methods, however, suffer from several drawbacks: poor yields are often obtained, a multiplicity of products is common, and reaction conditions may be inimical to other ring substituents. For example, methyl chloroformate, when treated with pyrrylmagnesium bromide or with pyrryllithium, gives small amounts of the desired methyl pyrrole-2-carboxylate and generally more of the 1 ester and 1,2 diester.[2] An unambiguous and better procedure involves the alkaline silver oxide oxidation of 2-formylpyrrole to the carboxylic acid.[2] This route also requires subsequent esterification; however, it can be avoided by conversion of the aldehyde to oxime, dehydration to nitrile, and acid-catalyzed alcoholysis to ester.[3] Recently a Friedel–Crafts type trichloroacetylation of pyrroles followed by hydrolysis of the trichloroacetyl group to carboxyl by treatment with sodium hydroxide has been reported.[4a] Similarly, the synthesis in high yield of pyrrole-2-carboxylic acid has been effected through the trifluoroacetyl moiety.[4b] However, the conversion of these pyrrole acids to esters again requires esterification which may prove limiting.

We hoped to develop a method that could introduce a wide variety of esters unambiguously and under mild conditions into pyrroles having varying substitution patterns. Functionalization of dipyrrylmethanes was likewise of interest, and here in particular the possible conditions are severely limited. The usual procedures mentioned above, involving metallopyrryl reagents or oxidation, cannot be used with dipyrrylmethanes because of the multiplicity of products from the former and the sensitivity of the methylene bridge to the latter. Furthermore, since rearrangement of dipyrrylmethanes may readily occur in acid,[5] neutral or mildly alkaline conditions were necessary.

Results

Trichloroacetylation.—We decided to explore the possibilities of using the trichloroacetyl (TCA) group, but, to avoid the Friedel–Crafts acylation with trichloroacetyl chloride (TCAC) and the concomitant strong acid conditions, we attempted a Vilsmeier acylation with *N*,*N*-diethyltrichloroacetamide. Since 2-chloroacetylpyrrole had been obtained in this manner from pyrrole and *N*,*N*-diethylchloroacetamide,[6] a precedent existed. Although we successfully repeated the synthesis of 2-chloroacetylpyrrole, Vilsmeier acylation afforded no 2-dichloroacetylpyrrole or 2-trichloroacetylpyrrole (2-TCA-pyrrole).

We were thus faced with the necessity of carrying out the trichloroacetylation with TCAC and, in contrast to the previous use of this reagent,[3] scavenging the acid produced with a suitable base, sufficiently strong to neutralize all the acid, but unreactive to TCAC. Such conditions were obtained by adding a solution of pyrrole and 2,6-lutidine in chloroform to a refluxing chloroform solution of TCAC. An 80% yield of pure 2-TCA-pyrrole resulted and, although some 1-TCA-pyrrole was observed, it was less than 10% of the product and was easily separated by silica gel chromatography.

This procedure now was applied to 2,4-dimethylpyrrole as a model that would more closely reflect the reactivity of the dipyrrylmethanes that we anticipated using. The yields of 2-TCA-3,5-dimethylpyrrole were poor, <20%, and proportionately greater fractions of the 1-TCA-2,4-dimethylpyrrole were formed. Other hindered amines [1,8-bis(dimethylamino)naphthalene, 1,2,2,6,6-pentamethylpiperidine] were also unsuitable. A highly convenient procedure was developed using potassium carbonate as an insoluble phase with TCAC in chloroform to which 2,4-dimethylpyrrole was added at room temperature. This method gave a 75% yield of 2-TCA-3,5-dimethylpyrrole and also was applicable to pyrrole.

These conditions were now examined for the trichloroacetylation of dipyrrylmethanes. Since we wished to test not only whether acylation would take place, but also whether potassium carbonate would inhibit acid-induced scrambling, a suitably unsymmetrical methane was needed. This was available

(1) This research was supported in part by Grant AI-04888 from the National Institutes of Health, U. S. Public Health Service.

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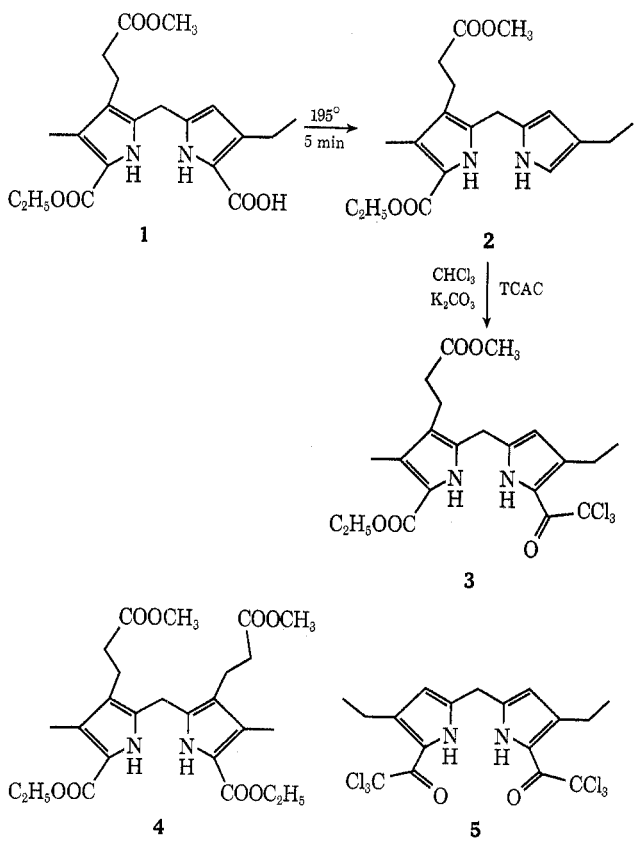
TABLE I

CONVERSION OF TCA-PYRROLES TO PYRROLE ESTERS

Expt	Compd	Alcohol	Base	Temp, °C	Time	Yield, %[a] Uv	Yield, %[a] Isolated
1	2-TCA-pyrrole	CH_3OH	CH_3O^-	25	1 min	100	88
2	2-TCA-pyrrole	CH_3OH	TEA[b]	65	20 min	100	
3	2-TCA-pyrrole	CH_3OH	TEA	25	70 hr	93	
4	2-TCA-pyrrole	C_2H_5OH	TEA	75	20 hr	97	
5	2-TCA-pyrrole	CH_2=$CHCH_2OH$	TEA	60	38 hr	97	77
6	2-TCA-pyrrole	CH_2=$CHCH_2OH$	K_2CO_3	60	1 hr	100	66
7	2-TCA-pyrrole	$(CH_3)_2C$=$CHCH_2OH$	TEA	60	62 hr	96	72
8	2-TCA-pyrrole	$C_6H_5CH_2OH$	TEA	60	38 hr	98	92
9	2-TCA-pyrrole	$(CH_3)_2CHOH$	$(CH_3)_2CHO^-$	80	2.5 hr		15
10	*c*	CH_3OH	TEA	65	3 min	100	25
11	*d*	$C_6H_5CH_2OH$	K_2CO_3	60	15 min	100	81
12	3,5-Dimethyl-2-TCA-pyrrole	Cl_3CCH_2OH	K_2CO_3	60	4.2 hr	100	74
13	3,5-Dimethyl-2-TCA-pyrrole	$ClCH_2CH_2OH$	K_2CO_3	60	3 hr	100	66

[a] Based on ratio of starting material and product absorbances. [b] Triethylamine. [c] Ethyl 3-methyl-4-isopropyl-5-trichloroacetyl-2-pyrrolecarboxylate. [d] Compound 9.

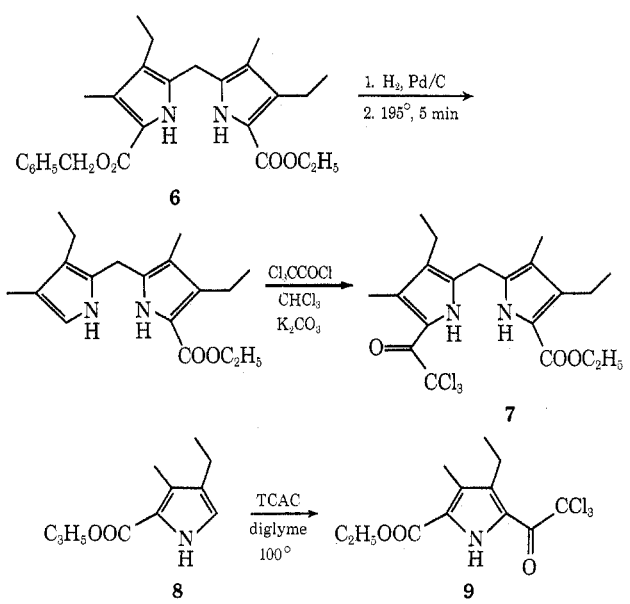
in the form of **2**, obtained from **1**,[7] with a substituent pattern typical of methanes useful in porphyrin syntheses. When dipyrrylmethane **2** was added to TCAC–potassium carbonate in chloroform as above, a single pure (tlc) compound was obtained which showed the expected nmr and uv spectral characteristics and the proper mass spectrum for structure **3**. Nonetheless, this did not completely rule out the presence of the rearranged methanes **4** and **5**, since **3**, **4**, and **5** all have as molecular ion *m/e* 490. However, the M^+, M + 2, and M + 4 peaks of the product were in the proper ratio required for three chlorines, and high-resolution mass spectroscopy shows that the *m/e* 490 peak is only the desired methane **3**.



(7) Prepared by D. Bergstrom, Ph.D. Thesis, University of California, Berkeley, 1970.

Since rearrangement had not occurred under the conditions of trichloroacetylation, we now applied this procedure to another dipyrrylmethane of interest as a porphyrin intermediate. Methane **6**[7] was hydrogenolyzed, decarboxylated, and trichloroacetylated. The trichloroacetylation was carried out with a threefold excess of TCAC and a 15-fold excess of carbonate. The product was obtained crude in quantitative yield and in 70% yield as pure material after crystallization.

To extend the generality of the reaction we examined an example of trichloroacetylation of an α-free α'-ethoxycarbonylpyrrole, since successful trichloroacetylation has been reported[8] only for β-carboethoxy pyrroles. When ethyl 3-methyl-4-ethyl-2-pyrrolecarboxylate was heated with a fivefold excess of TCAC in dry diglyme, the uv soon indicated complete reaction and after chromatography a 75% yield of pure trichloroacetylated product **9** was obtained as a light yellow oil.



Alcoholysis of Trichloroacetylpyrroles.—Trichloroacetylpyrroles have been successfully converted to the corresponding pyrrole acids by heating in aqueous sodium hydroxide.[8] This reaction undoubtedly involves hydroxide ion attack at the carbon of the tri-

chloroacetyl carbonyl followed by trichloromethyl anion elimination. If this mode of reaction could be extended to alcohols it would lead directly to pyrrole esters, which are much more useful synthetic intermediates than the acids. The first choice was to attempt preparation of methyl esters, and we found that methanol and methoxide at room temperature affected instantaneous and quantitative conversion of 2-TCA-pyrrole to 2-methoxycarbonylpyrrole. Triethylamine (TEA) and refluxing methanol also affected the conversion rapidly, the half-life being less than 5 min.

Table I indicates the conversions that have been carried out. The reaction is greatly influenced by the steric factors in the alcohol as well as the base, as methanol reacts extremely rapidly in this haloform-type reaction, but other alcohols behave much more sluggishly. Isopropyl alcohol reacts only poorly with TEA as base; with alkoxide the reaction proceeds fairly rapidly, but is accompanied by much darkening and formation of side products. *tert*-Butyl alcohol reacted not at all even with the most effective alkoxide catalyst.

The reactions utilizing potassium carbonate as base point out again the value of this heterogeneous system. The rate of ester formation is much greater than with TEA, no darkening of the reaction occurs, the base is easily removed, and the conditions are still much milder than with alkoxide catalyst. Of particular interest are entries 10 and 11, where the advantage of the mild base is well demonstrated. The diesters were obtained with no contamination of the preexisting ethyl esters whatsoever. These reactions were all conducted on a small scale and were admirably suited for uv monitoring, the absorption maximum shifting cleanly from 312 to around 265 nm for the monosubstituted and from 317 to around 282 nm for the fully substituted pyrroles.

Another possible utilization of the difunctionality is the selective conversion of trichloroacetyl to carboxyl. This conversion has been accomplished by heating in sodium hydroxide, which does not hydrolyze β-ethoxycarbonyl groups.[3] However, since α-ethoxycarbonyl groups are much more susceptible to alkaline hydrolysis,[8] we preferred to operate at lower pH. When ethyl 3-methyl-4-ethyl-5-trichloroacetyl-2-pyrrolecarboxylate (**9**) was heated in aqueous potassium carbonate for less than 2 min the trichloroacetyl group was converted to carboxyl with no loss of ethyl ester. Potassium bicarbonate took 45 min but the results were similar; isolated yields in the two cases were 91 and 87%, respectively. These two reagents also convert 2-TCA-pyrrole to 2-pyrrolecarboxylic acid, but not quite so rapidly. With potassium carbonate the reaction was complete in 25 min using the concentrations of the above experiment.

A recent publication[4] described the improved synthesis of trifluoroacetylpyrroles using trifluoroacetic anhydride with dimethylaniline as an acid scavenger. Attempted extension of the alcoholysis reaction to TFA pyrroles was unsuccessful. Although these compounds could be converted to the corresponding acid with hydroxide, alcoholysis under a variety of conditions gave at best less than 20% yield of the desired ester.

Thus trichloroacetylation of pyrroles, in the presence of an acid scavenger where necessary, and subsequent treatment with an alcohol and mild base, is a convenient method for directly introducing an ester group into the pyrrole nucleus. The trichloroacetylation reaction gives good yields when the pyrrole ring is unsubstituted, alkyl substituted, or α- or β-ethoxycarbonyl substituted. Alcoholysis to ester, which proceeds in synthetically useful yields with primary alcohols, takes place readily in the presence of a tertiary amine or potassium carbonate, and other ester groups in the molecule are unaffected. Also, pyrrole acids may be prepared from TCA-pyrroles in the presence of other nuclear ester groups without affecting these preexisting esters using carbonate reagents.

Experimental Section[9]

2-Trichloroacetylpyrrole.—To a refluxing solution of 14 ml of chloroform and 3.24 ml (5.38 g, 29.5 mmol) of trichloroacetyl chloride was added over 60 min a solution of 1.85 ml (1.80 g, 26.8 mmol) of pyrrole and 3.43 ml (3.15 g, 29.5 mmol) of 2,6-lutidine in 14 ml of chloroform. Refluxing was continued for 15 min, the solvent was evaporated, ether was added, and the mixture was filtered. The light-yellow filtrate was washed twice with 3 *N* HCl and thrice with water, dried, and evaporated, giving a crude yield of 5.69 g (100%). Chromatography on silica gel, elution with chloroform, and recrystallization from hexane gave pure trichloroacetylpyrrole: yield 4.54 g (80%); mp 73.5–74° (lit.[3] mp 70°); uv 312 nm (ϵ 13,400); nmr (CCl_4) δ 6.27 (m, 1), 7.12 (m, 1), 7.31 (m, 1), 10.4 (br s, 1); mass epectrum *m/e* (rel intensity) 215 (4), 213 (13), 211 (M^+, 15), 150 (7), 149 (4), 148 (11), 95 (6), 94 (100), 66 (17).

3,5-Dimethyl-2-trichloroacetylpyrrole.—To 8.55 g (62 mmol) of anhydrous potassium carbonate, 20 ml of chloroform, and 1.71 ml (15.5 mmol) of TCAC was added over 65 min a solution of 1.81 g (12.4 mmol) of 2,4-dimethylpyrrole in 10 ml of chloroform. After completion of the addition, the mixture was filtered, the solid was washed with chloroform, the combined washings and filtrate were washed once with saturated $NaHCO_3$ solution, once with water, and thrice with brine, and the solution was evaporated, leaving a residue of 2.94 g (99%). Chromatography on silica gel, elution with chloroform, and recrystallization from hexane gave 2.23 g (75%) of 3,5-dimethyl-2-trichloroacetylpyrrole: mp 107–108° (lit.[3] mp 106–107°); uv 324 nm (ϵ 15,600); nmr δ 2.32 (s, 3), 2.41 (s, 3), 5.92 (m, 1), 8.8 (br s, 1); mass spectrum *m/e* (rel intensity) 243 (5), 241 (15), 239 (M^+, 16), 178 (7), 176 (10), 123 (8), 122 (100), 94 (4), 67 (7).

1-Trichloroacetyl-2,4-dimethylpyrrole was isolated as the first fraction on chromatography of the trichloroacetylation mixture: nmr δ 2.00 (s, 3), 2.45 (s, 3), 5.85 (m, 1), 7.27 (m, 1); mass spectrum *m/e* (rel intensity) 241 (6), 239 (M^+, 8), 206 (6), 205 (5), 204 (9), 122 (7), 95 (5), 94 (100), 67 (9).

Ethyl 3-Methyl-4-ethyl-5-trichloroacetyl-2-pyrrolecarboxylate (**9**).—A solution of 1.15 g (6.4 mmol) of ethyl 3-methyl-4-ethyl-2-pyrrolecarboxylate (**8**), 9.0 ml of diglyme, and 3.49 ml (31.7 mmol) of TCAC was stirred at 100° for 19 hr. The reaction mixture was then poured into ice water and diluted with ether, and the layers were separated. The ether was washed twice with water, twice with bicarbonate, and twice with brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel, eluting with chloroform, gave 1.55 g (75%) of a pale yellow oil: uv 317 and 236 nm; nmr δ 1.13 (t, 3), 1.40 (t, 3), 2.34 (s, 3), 2.82 (q, 2), 4.38 (q, 2), 9.7 (br s, 1); mass spectrum *m/e* (rel intensity) 329 (3), 327 (10), 325 (M^+, 10), 290 (6), 209 (14), 208 (100), 163 (10), 162 (85).

(8) A. H. Corwin and J. L. Straughn, *J. Amer. Chem. Soc.*, **70**, 1416 (1948).

(9) Melting points are uncorrected. Microanalyses were obtained from the Analytical Laboratory, College of Chemistry, University of California. Spectra were obtained with a Varian T-60 nmr spectrometer (reported as δ values in $CDCl_3$ unless otherwise specified); a Cary 14 uv-visible spectrometer (reported in nanometers in 95% ethanol); and CEC Type 21, 103-C, and AEI MS-12 mass spectrometers.

Anal. Calcd. for $C_{12}H_{14}NO_3Cl_3$: C, 44.2; H, 4.3. Found: C, 43.8; H, 4.3.

4-Methyl-3′-ethyl-3-(β-methoxycarbonylethyl)-5-ethoxycarbonyl-5′-trichloroacetyl-2,2′-dipyrrylmethane (3).—The corresponding methane-5′-carboxylic acid **1** (27 mg, 0.069 mmol)[7] was heated at 195° for 5 min to effect decarboxylation and the decarboxylated methane **2**, dissolved in 2.0 ml of chloroform, was added to 127 mg (0.92 mmol) of potassium carbonate and 2.0 ml of chloroform containing 12.3 μl (0.112 mmol) of TCAC. The mixture in the flask was stirred at room temperature as the solution of **2** was added over 70 min. During and after the addition, another 30 μl (0.29 mmol) of TCAC was added and the mixture was heated at reflux for 30 min, during which time no change was observed in uv peak ratios. The reaction mixture was filtered, the filtrate was washed once with saturated bicarbonate, twice with brine, dried, and evaporated, and the residue was chromatographed on silica gel, eluting with chloroform. A 12-mg (35%) fraction contained the pure product, dipyrrylmethane **3**: uv 326 and 278 nm; nmr δ 1.20 (t, 3), 1.32 (t, 3), 2.26 (s, 3), 2.6 (m, 6), 3.62 (s, 3), 4.03 (s, 2), 4.22 (q, 2), 6.05 (d, 1), 9.1 (br s); mass spectrum *m/e* (rel intensity) 494 (1), 492 (2), 490 (M^+, 2), 456 (37), 454 (44), 421 (33), 420 (52), 384 (30), 383 (48), 372 (41), 345 (37), 299 (100). High resolution mass spectrum calcd for $C_{21}H_{25}N_2O_5Cl_3$: 490.0829. Found: 490.0835.

3,4′-Dimethyl-3′,4-diethyl-5-ethoxycarbonyl-5′-trichloroacetyl-2,2′-dipyrrylmethane (7).—Hydrogenolysis of the 5′-*o*-chlorobenzyloxycarbonyl compound **6**[7] gave the 5′-carboxy compound, and 254 mg (0.73 mmol) of this acid was decarboxylated by heating for 3 min at 198°. The resulting oil was dissolved in 3.0 ml of chloroform and added to 1.45 g (11.0 mmol) of potassium carbonate, 5.0 ml of chloroform, and 242 μl (2.20 mmol) of TCAC with vigorous stirring over 50 min. Stirring was continued for another 15 min, and then the mixture was poured into saturated $NaHCO_3$ solution and diluted with chloroform, and the layers were separated. The organic phase was washed twice with brine, dried ($MgSO_4$), and evaporated, giving 325 mg (99%) of a reddish-brown solid which was recrystallized from hexane: yield 231 mg (70%) of needles; mp 151–153°; uv 335 nm (ε 17,100), 279 (20,500); nmr δ 1.07 (t, 3), 1.11 (t, 3), 1.28 (t, 3), 1.95 (s, 3), 2.34 (s, 3), 2.46 (q, 2), 2.70 (q, 2), 3.98 (s, 2), 4.18 (q, 2), 9.03 (br s, 1), 10.00 (br s, 1); mass spectrum *m/e* (rel intensity) 450 (4), 448 (10), 446 (M^+, 11), 414 (8), 412 (12), 330 (26), 329 (100), 274 (11), 273 (49).

Anal. Calcd for $C_{20}H_{25}N_2O_3Cl_3$: C, 53.6; H, 5.6; N, 6.3. Found: C, 53.7; H, 5.5; N, 6.5.

Methyl 2-Pyrrolecarboxylate.—2-TCA-pyrrole (101 mg, 0.48 mmol) was added to a solution of 26 mg (1.1 mg-atoms) of sodium in 11 ml of methanol. Reaction was immediate and the solution was evaporated to dryness, the residue was partitioned between ether and water, and the ether was washed three times with water, dried and evaporated, leaving 52 mg (88%) of crystals which were recrystallized from hexane: mp 69–70° (lit.[10] mp 72–73°); uv 265 nm (ε 15,400); nmr δ 3.80 (s, 3), 6.22 (m, 1), 6.95 (m, 2), 10.1 (br s, 1); mass spectrum *m/e* (rel intensity) 126 (7), 125 (M^+, 100), 95 (7), 94 (98), 94 (30), 66 (17), 65 (9), 39 (23), 38 (7).

Allyl 2-Pyrrolecarboxylate.—2-TCA-pyrrole (424 mg, 2.00 mmol) was dissolved in 0.68 ml (0.58 g, 10.0 mmol) of allyl alcohol, 0.35 ml (0.25 g, 2.5 mmol) of triethylamine was added, and the solution was heated at 60° for 38 hr. The solvent was evaporated, the residue was partitioned between ether and water, the aqueous layer was twice extracted with ether, and the combined ether layers were washed with three portions of water, dried ($MgSO_4$), and evaporated, giving 288 mg (95%) of brown oil. This was distilled (10 mm, 90°) onto a cold finger to give 231 mg (77%) of the allyl ester: uv 265, 229 nm; nmr δ 4.73 (d, 2), 5.2 (m, 2), 5.8 (m, 1), 6.20 (m, 1), 6.87 (m, 2); mass spectrum *m/e* (rel intensity) 151 (M^+, 42), 106 (6), 95 (11), 94 (100), 93 (18), 86 (23), 77 (8), 76 (15), 41 (15), 39 (15).

Anal. Calcd for $C_8H_9NO_2$: C, 63.6; H, 6.0; N, 9.3. Found C, 63.3; H, 6.1; N, 9.1.

γ,γ-Dimethylallyl 2-Pyrrolecarboxylate was prepared from 2-TCA-pyrrole, dimethylallyl alcohol, and triethylamine, as described for the allyl ester, by heating for 62 hr. Distillation (10 mm, 90°) onto a cold finger gave a 72% yield of the β,β-dimethylallyl ester: uv 265 and 229 nm; nmr (CCl_4) δ 1.75 (s, 6), 4.68 (d, 2), 5.36 (m, 1), 6.07 (m, 1), 6.78 (m, 2), 10.3 (br s, 1); mass spectrum *m/e* (rel intensity) 180 (12), 179 (M^+, 90), 150 (11), 112 (21), 111 (100), 94 (71), 93 (86), 69 (58), 68 (18), 67 (24), 66 (23).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3. Found: C, 66.6; H, 7.2.

Benzyl 2-pyrrolecarboxylate was prepared from 2-TCA-pyrrole and benzyl alcohol using the triethylamine procedure above and heating for 38 hr. The benzyl ester was obtained in 92% yield on crystallization from hexane: mp 54–55°; uv 267 nm (ε 18,000), 236 (4900), nmr δ 5.27 (s, 2), 6.21 (m, 1), 6.89 (m, 2), 7.32 (s, 5), 9.7 (br s, 1); mass spectrum *m/e* (rel intensity) 202 (15), 201 (M^+, 100), 94 (29), 92 (9), 91 (91).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5. Found: C 71.6; H, 5.4.

Isopropyl 2-Pyrrolecarboxylate.—Sodium (123 mg, 5.35 mg-atoms) was dissolved in 30 ml (200 mmol) of isopropyl alcohol and heated to 70°, and 1.0 g (4.7 mmol) of 2-TCA-pyrrole was added. The temperature was raised to 80° for 2.5 hr, the solvent was evaporated, the residue was partitioned between ether and water, and the ether layer was washed thrice with water, dried ($MgSO_4$), and evaporated. Silica gel–chloroform chromatography of the residue and sublimation gave 109 mg (15%) of the isopropyl ester: mp 32–34°; uv 265 nm (ε 16,800), 235 (4800); nmr δ 1.32 (d, 6, J = 9 Hz), 5.18 (m, 1), 6.20 (m, 1), 6.88 (m, 2); mass spectrum *m/e* (rel intensity) 153 (M^+, 30), 111 (50), 94 (45), 93 (100), 67 (8), 66 (19), 65 (9).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.7; H, 7.2. Found: C, 62.6; H, 7.2.

2-Ethoxycarbonyl-5-methoxycarbonyl-3-methyl-4-propylpyrrole was prepared from ethyl 3-methyl-4-propyl-5-trichloroacetyl-2-pyrrolecarboxylate and methanol using the triethylamine procedure above and heating at 90° for 20 min. Crystallization from hexane gave a 25% yield of the 5-methoxycarbonyl compound: mp 41–42°; uv 282 nm; nmr δ 0.91 (t, 3), 1.36 (t, 3), 2.07 (s, 3), 2.72 (t, 2), 3.85 (s, 3), 4.35 (q, 2); mass spectrum *m/e* (rel intensity) 254 (9), 253 (M^+, 57), 225 (18), 224 (100), 222 (6), 208 (7), 192 (8), 179 (11), 178 (85), 176 (16), 174 (16), 174 (7), 148 (9), 146 (9).

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.4; H, 7.6; N, 5.5.

2-Benzyloxycarbonyl-5-ethoxycarbonyl-3-ethyl-4-methylpyrrole.—Ethyl 3-methyl-4-ethyl-5-trichloroacetyl-2-pyrrolecarboxylate (**9**), 425 mg (1.30 mmol), 0.70 g (6.5 mmol) of benzyl alcohol, and 225 mg (1.62 mmol) of potassium carbonate were heated at 60° for 15 min. The reaction mixture was diluted with ether and filtered, and the filtrate was washed twice with salt solution, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel, eluting with benzene, to yield 330 mg (81%) of the benzyl ester: mp 47–50°; uv 283 nm (ε 22,800), 221 (17,800), 218 (18,000); nmr δ 1.08 (t, 3), 1.28 (t, 3), 2.24 (s, 3), 2.72 (q, 2), 4.26 (q, 2), 5.27 (s, 2), 7.31 (s, 5), 9.81 (br s, 1); mass spectrum *m/e* (rel intensity) 316 (15), 315 (M^+, 63), 270 (13), 269 (8), 226 (6), 225 (16), 224 (100), 208 (26), 206 (13), 178 (16), 162 (22), 160 (15), 149 (21), 111 (15), 97 (16), 95 (14), 91 (88).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.6; H, 6.7; N, 4.4. Found: C, 68.6; H, 6.6; N, 4.3.

β,β,β-Trichloroethyl 3,5-dimethyl-2-pyrrolecarboxylate was prepared from 3,5-dimethyl-2-trichloroacetylpyrrole and β,β,β-trichloroethanol using the potassium carbonate procedure described above. Crystallization from petroleum ether (bp 30–60°) gave the β,β,β-trichloroethyl ester in 74% yield: mp 126–128°; uv 281 nm (ε 22,900), 249 (4900); nmr (CCl_4) δ 8.8 (br s, 1), 5.70 (d, 1, J = 3 Hz), 4.84 (s, 2), 1.97 (s, 3), 1.93 (s, 3); mass spectrum m/e (rel intensity) 275 (4), 273 (30), 271 (100), 269 (99), 238 (2), 236 (12), 234 (19), 138 (19), 122 (93), 121 (95), 94 (7), 93 (8).

Anal. Calcd for $C_9H_{10}Cl_3NO_2$: C, 40.0; H, 3.7; N, 5.2. Found: C, 40.3; H, 3.9; N, 5.3.

β-Chloroethyl 3,5-dimethyl-2-pyrrolecarboxylate was prepared by the potassium carbonate procedure, using excess 2-chloroethanol, at 60° for 2 hr. The mixture was cooled, diluted with ether, and filtered, and the filtrate was washed twice with brine, dried ($MgSO_4$), and evaporated. Crystallization of the residue from hexane gave pure ester in 66% yield: mp 79–82°; uv 278 nm (ε 20,500), 248 (4800); nmr δ 2.23 (s, 3), 2.30 (s, 3), 3.70 (t, 2), 4.47 (t, 2), 5.78 (d, 1), 9.4 (br s, 1); mass spectrum *m/e* (rel intensity) 203 (15), 201 (M^+, 48), 166 (12), 139 (45), 138 (34), 123 (12), 122 (100), 121 (98), 120 (46), 95 (23), 94 (51), 93 (59), 92 (28), 67 (67), 66 (77), 65 (59), 64 (10), 63 (22).

(10) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 1, Akad. Verlags., Leipzig, 1934, p 237.

Anal. Calcd for $C_9H_{12}ClNO_2$: C, 53.6; H, 6.0; N, 7.0. Found: C, 53.4; H, 5.9; N, 7.0.

5-Ethoxycarbonyl-3-ethyl-4-methyl-2-pyrrolecarboxylic Acid.—The corresponding 5-trichloroacetylpyrrole **9** (233 mg, 0.71 mmol) was heated at 100° with 1.97 g (14.3 mmol) of potassium carbonate in 3 ml of water for 5 min. Cooling and acidification to pH 5.5 gave 145 mg (91%) of the acid, mp 214–217° (lit.[10] mp 211°).

In the same manner, but heating with a potassium bicarbonate solution for 45 min, an 87% yield of the acid was obtained: uv 283 and 217 nm; nmr δ 1.03 (t 3), 1.30 (t, 3), 2.20 (s, 3), 2.68 (q, 2), 4.23 (q, 2), 8.8 (br s, 1), 11.23 (br s, 1).

Registry No.—**3**, 35889-82-8; **7**, 35889-83-9; **9**, 35889-84-0; allyl 2-pyrrolecarboxylate, 35889-85-1; γ,γ-dimethylallyl 2-pyrrolecarboxylate, 35889-86-2; benzyl 2-pyrrolecarboxylate, 35889-87-3; isopropyl 2-pyrrolecarboxylate, 35889-88-4; 2-ethoxycarbonyl-5-methoxycarbonyl-3-methyl-4-propylpyrrole, 35889-89-5; 2-benzyloxycarbonyl-5-ethoxycarbonyl-3-ethyl-4-methylpyrrole, 35889-90-8; β,β,β-trichloroethyl 3,5-dimethyl-2-pyrrolecarboxylate 35889-91-9; β-chloroethyl 3,5-dimethyl-2-pyrrolecarboxylate, 35889-92-0.

A Direct Synthesis of 2-Acylindoles

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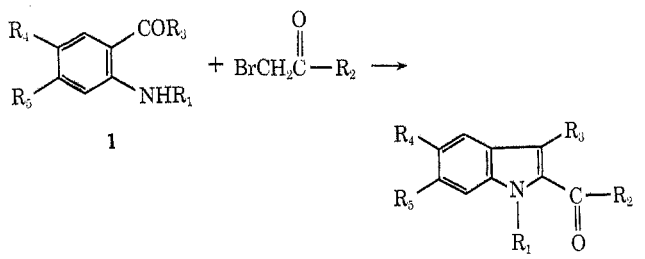
o-Aminocarbonyl compounds have been found to undergo direct and facile conversion to 2-acylindoles upon heating with α-halo ketones in dimethylformamide. A variety of *o*-aminoacetophenones and *o*-aminobenzophenones gave the corresponding 2-acyl-3-methyl- and 2-acyl-3-phenylindoles, respectively. Although *o*-aminobenzaldehyde did not undergo this reaction, use of the derived ethylene acetal permitted preparation of the 3-unsubstituted 2-acylindole in moderate yield. The overall indole formation is presumed to proceed *via* N-alkylation, followed by intramolecular aldol condensation and dehydration. Chemical evidence in support of this hypothesis is presented.

Although the direct assemblage of 2-acylindoles, depicted by the transformation of **1** → **2**, represents an



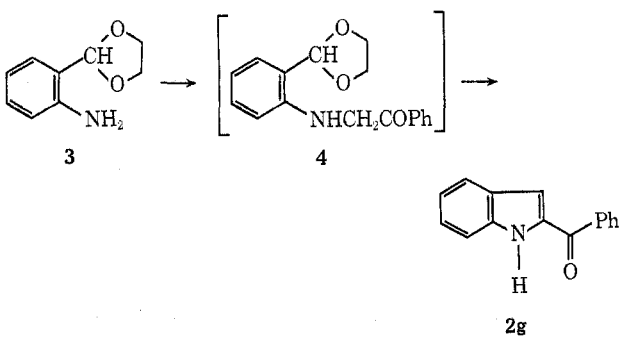
1 **2**

attractive route to the indole nucleus, this conversion has not been exploited to any great degree.[1] Our need for 2-acylindoles for use in a related problem prompted us to examine this reaction in some detail. In this paper we wish to report a convenient method for the transformation of *o*-amino ketones into 2-acylindoles under mild reaction conditions and in good yield.

In a preliminary experiment, equivalent quantities (0.5 mmol) of *o*-aminobenzophenone and phenacyl bromide dissolved in DMF-d_7 were heated together at 80° for 12 hr. Periodic observation of the nmr spectrum of the mixture revealed a loss of the halo ketone methylene singlet at δ 4.94. A broad one-proton signal appeared at δ 11.90, attributable to the NH proton of 2-benzoyl-3-phenylindole (**2a**). When the reaction was repeated on a preparative scale, crystalline **2a** was obtained in 73% yield (Table I), and its structure was fully characterized spectroscopically.

Further efforts to evaluate the scope of the reaction first concerned the effect of substituents in the *o*-amino ketone moiety. Under the same reaction conditions, the appropriate *o*-aminobenzophenones formed 5-chloro- (**2b**), 6-chloro- (**2c**), and 5,6-dimethoxyindole (**2d**) in good yields, thereby demonstrating the tolerance of the reaction for diverse aromatic substituents. Furthermore, the indole formation proceeded equally well with *N*-alkyl-*o*-amino ketones, as shown by the formation of 1-methyl-2-benzoyl-3-phenylindole (**2e**), also in good yield.

Particular attention was warranted concerning the variation of R_3 substituents since 2-acylindoles lacking substituents at the 3 position are often difficult to prepare by available means. The reaction of *o*-aminoacetophenone and phenacyl bromide yielded under the usual conditions 2-benzoyl-3-methylindole (**2f**). However, when treated similarly, *o*-aminobenzaldehyde gave an intractable tar to the virtual exclusion of indole formation. Nevertheless, by modifying reactants and reaction conditions, it was possible to prepare the 3-unsubstituted derivative. To this end, acetal **3** was alkylated with phenacyl bromide in the presence of 1 equiv of $NaHCO_3$. Subsequent acidification and heating cleaved the presumed intermediate acetal (**4**) and also effected condensation to 2-benzoylindole (**2g**).



3 **4** **2g**

Chemical evidence that reactions of this type proceed *via* the expected N-alkylation, followed by condensation, was obtained in the preparation of **2f**. In this example, cyclization of intermediate **6** to the indole is the rate-limiting step. Thus, heating the reactants

(1) To our knowledge, only α-bromo diketones have been converted to indoles by this reaction; see G. Kempter and E. Schiewald, *J. Prakt. Chem.*, **28**, 169 (1965), and R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).