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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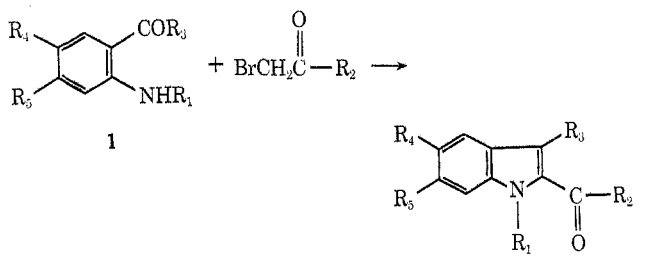
o-Aminocarbonyl compounds have been found to undergo direct and facile conversion to 2-acylindoles upon heating with α-halo ketones in dimethylformamide. A variety of *o*-aminoacetophenones and *o*-aminobenzophenones gave the corresponding 2-acyl-3-methyl- and 2-acyl-3-phenylindoles, respectively. Although *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



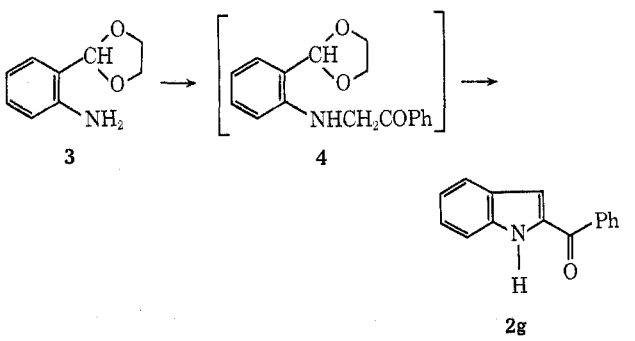
1 **2**

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

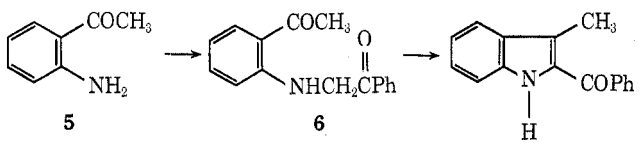
(1) To our knowledge, only α-bromo diketones have been converted to indoles by this reaction; see G. Kempter and E. Schiewald, *J. Prakt. Chem.*, **28**, 169 (1965), and R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

TABLE I
2-ACYLINDOLES[a]

Compd	R_1	R_2	R_3	R_4	R_5	Recrystn solvent	Mp, °C	% yield
2a	H	Ph	Ph	H	H	MeOH	203–204 (lit.[b] 203.5–5.0)	73
2b	H	Ph	Ph	Cl	H	MeOH	194–195	75
2c	H	Ph	Ph	H	Cl	MeOH	198–199	70
2d	H	Ph	Ph	OCH_3	OCH_3	MeOH	211–212	50
2e	CH_3	Ph	Ph	H	H	Hexane	87–88	71
2f	H	Ph	CH_3	H	H	MeOH	138–139 (lit.[c] 140)	69
2g	H	Ph	H	H	H	MeOH	147–148 (lit.[d] 146–148)	60
2h	H	CH_3	Ph	H	H	MeOH	150–151 (lit.[e] 151)	69

[a] Satisfactory analytical values (±0.4 % for C, H, N) were reported for compounds **2b–e**: Ed. [b] D. Y. Curtin, M. L. Poutsma, *J. Amer. Chem. Soc.*, **84**, 4887 (1962). [c] V. I. Shvedov, V. V. Alekseev and A. N. Grinev, *Khim-Farm. Zh.*, **2**, 8 (1968); *Chem. Abstr.*, **70**, 11469f (1969). [d] R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965). [e] Reference 2.

for a relatively short period yielded the uncyclized intermediate **6**. With further heating, **6** converted easily into the expected indole **2f**.



5 **6** **2f**

Modifications of R_2 are important since the removal of the 2-acyl group would provide a synthesis of the parent indoles. The successful reaction of bromoacetone with *o*-aminobenzophenone to provide the 2-acetyl derivative **2h** proves that the alkylation–cyclization sequence applies to both alkyl- and aryl bromomethyl ketones. The deacetylation of **2h** to the parent 3-phenylindole has already been reported.[2]

In conclusion, the alkylation–condensation sequence between *o*-amino ketones and α-bromo ketones provides ready access to a wide variety of 2-acylindoles. Removal of the 2-acetyl group gives rise to the parent indoles themselves. We are continuing our efforts regarding the more easily removable functions at the 2 position and the application of this method to the synthesis of indoles of biological significance.

Experimental Section

All melting points were taken in a Mel-Temp capillary melting point block and are uncorrected. Nmr spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ or DMF-d_7 using TMS as internal reference. Except for compound **2g**, the following general procedure was used for all of the 2-acylindoles in Table I. Satisfactory analytical data has been obtained for all new compounds.

General Procedure.—The *o*-amino ketone (0.02 mol) and the appropriate α-halo ketone (0.02 mol) were dissolved in 50 ml of anhydrous DMF, and the solution was heated in an oil bath (80–90°) for 16 hr. The reaction mixture was then poured over ice (1500 ml), and the crystalline 2-acylindole was isolated by filtration.

In those cases (**2e**, **2a**, and **2h**) where an oil was obtained, the product was extracted into ether (200 ml), and the ether layer was routinely washed with 48% HBr (10 ml), 5% $NaHCO_3$ (2 × 50 ml), and, finally, H_2O (50 ml). Drying the ether solution over $MgSO_4$, followed by evaporation, resulted in each instance in a yellow oil which was separated from polymeric material by column chromatography (1.5 in. × 8 in. silica gel using ether as the eluent). Trituration of the resultant products with MeOH or hexane gave the crystalline 2-acylindole. Analytical samples were prepared by recrystallization from MeOH or by vacuum sublimation.

Preparation of 3-Unsubstituted Derivatives.—Amino acetal **3**[3] (5.0 g, 0.03 mol) was alkylated when stirred in DMF (100 ml) at room temperature for 14 hr with phenacyl bromide (6.05 g, 0.03 mol) in the presence of $NaHCO_3$ (3 g, 0.035 mol). Then 0.5 cc of 48% HBr was added, and the mixture was heated at 80–90° for 24 hr. The reaction mixture was then poured over ice and worked up as described above to provide 4.0 g (60%) of 2-benzoylindole (**2g**). This material was characterized by its melting point as well as its nmr, ir, and uv spectra, each of which closely matched the corresponding values reported for 2-benzoylindole prepared by a different route.[4]

Isolation of Uncyclized Intermediate 6.—A solution of *o*-aminoacetophenone (5.0 g, 0.037 mol) and phenacyl bromide (7.35 g, 0.037 mol) in DMF (100 cc) was heated at 80–90° for 2 hr. The hot mixture was treated with water until slightly cloudy and then allowed to cool slowly. Precipitated yellow crystals were collected, washed with cold MeOH, and then recrystallized from the same solvent to provide 4.5 g (48%) of **6**: mp 131–132° nmr δ ($CDCl_3$) 2.54 (s, 3 H, $COCH_3$), 4.60 (d, 2 H, J = 4 Hz, $COCH_2N$), 6.45–6.75 (m, 2 H, Ar H), 7.10–8.10 (m, 7 H, Ar H), 10.40 (m, 1 H, NH); mass spectrum M^+ 253. *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 75.87; H, 5.97; N, 5.53; O, 12.63. Found: C, 75.78; H, 6.04; N, 5.57; O, 12.62.

Further heating of **6** (2 g) at 80–90° in 20 ml of DMF containing 0.5 cc of HBr for 16 hr gave the expected 2-benzoyl-3-methylindole (**2f**), mp 138–139°.

Registry No.—**2a**, 36004-54-3; **2b**, 36004-55-4; **2c**, 36004-56-5; **2d**, 36004-57-6; **2e**, 36004-58-7; **2f**, 1025-97-4; **2g**, 1022-86-2; **2h**, 36015-23-3; **3**, 26908-34-9; **6**, 36004-62-3.

(2) R. H. F. Manske, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* 1 (1927).

(3) This amino acetal was prepared by reduction of *o*-nitrobenzaldehyde ethylene acetal over Raney nickel in ethanol solution at 60° for 45 min. Although this compound decomposes on standing overnight at 25°, a freshly prepared sample gave the following spectra data: nmr δ ($CDCl_3$) 4.02 (s, 4 H, OCH_2CH_2O), 3.80–4.40 (broad, 2 H, NH_2), 5.77 (s, 1 H, ArCH<), 6.42–7.38 (m, 4 H, Ar H).

(4) Reference *d* in Table I.