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(14) Phosphonitrilic chloride–DMSO in HMPA–CH_2Cl_2 (−20°) oxidized **5** to **6** in 78% yield.

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Intramolecular Homoconjugate Addition. A Simple Entry to Functionalized Pyrrolizidines and Indolizidines

Summary: Intramolecular alkylation of amines by activated cyclopropanes, followed by lactam formation, gives functionalized bicyclic nitrogen heterocycles.

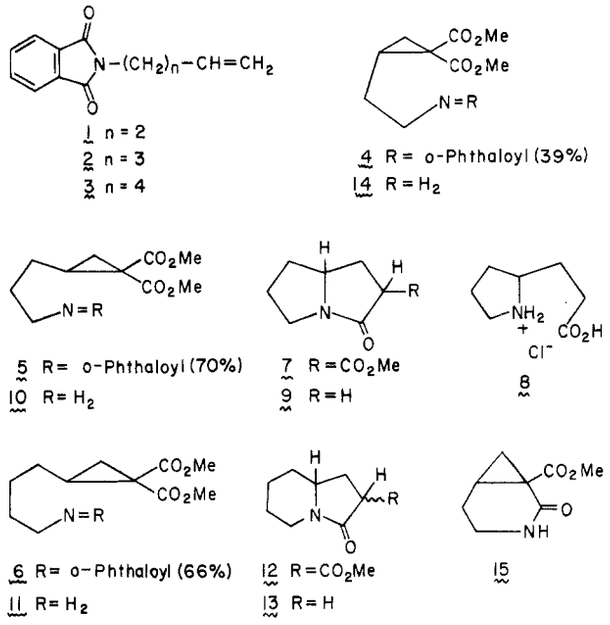
Sir: Recently we reported a new approach to the synthesis of functionalized carbocyclic ring system.[1] The method involves the generation of an anionic carbon center in juxtaposition with a cyclopropane ring which is so substituted as to render it vulnerable to nucleophilic attack. Below, we demonstrate the applicability of this concept to heterocyclic synthesis in the context of facile constructions of the pyrrolizidine[2] and indolizidine[2a] ring systems from readily available precursors.

The phthalimido olefins **1**,[3a] **2**,[3b] and **3**,[4a] mp 25.5–26.5°, were prepared by the alkylation of potassium phthalimide with 4-bromo-1-butene, 5-bromo-1-pentene, and 6-bromo-1-hexene, respectively. The cyclopropanes **4**,[4] mp 124–125°, **5**,[4] mp 84–85°, and **6**, mp[4] 91–92°, were prepared in the yields shown[5] by cyclopropanation of the corresponding olefins with dimethyl diazomalonate (*e.g.*, for the case of **4**, 0.107 mol of diazo compound added dropwise over 0.5 hr to a mixture of 0.094 mol of **1** and 130 mg of copper bronze which was heated at 140° under nitrogen).

Reaction of **5** with hydrazine (1.1 equiv of hydrazine to 1 equiv of **5** in methanol under reflux for 15 hr) gave the lactam ester **7**[4a] in quantitative recovery. Hydrolysis and decarboxylation of this compound (10% aqueous HCl, reflux 15 hr) is accompanied by ring opening. The pyrrolidine propionic acid salt, **8**, so produced,[6] was not purified. Esterification by MeOH–HCl produced the ester hydrochloride which was converted to the known[7] pyrrolizid-3-one (**9**) in 93% overall yield from **5**.

When the hydrazinolysis was conducted at room temperature, the intermediate amino diester **10** was isolated in 65% yield. Purification of **10**[4a] was rendered difficult by its tendency to undergo partial conversion to **7** on chromatography. Hence, for preparative purposes, direct conversion of **5** → **7** is the preferred method.

It appears reasonable to postulate that, in the pathway from **10** (or **5**) → **7**, internal alkylation of the amine by the activated cyclopropane occurs before lactamization. The reverse order of steps seems unlikely since it would require formation of a seven-membered lactam and, more seriously, necessitate an endocyclic[8] displacement during the alkylation step.



Preliminary experimentation revealed that the conditions required for conversion of amino diester **11**[4a] [obtained by room temperature hydrazinolysis (*cf.* above) of phthalimido diester **6**] to the epimeric indolizidine derivatives **12** are considerably more drastic than those required for the case of **10** → **7**. The considerably more facile formation of a pyrrolidine relative to a piperidine *via* intramolecular homoconjugate addition finds precedent in the carbocyclic series.[1] Hence, more vigorous hydrazinolysis conditions (1.1 equiv of hydrazine in MeOH at 115°, sealed tube, 15 hr) were employed for the conversion of **6** → **12**. The known epimeric mixture[9] thus obtained in crude form was carried through the same sequence of reactions as for the case of **7** to give 3-indolizidone **13**[7] in 82% overall from **6**. By the same reasoning set forth in the case of **10**, the most likely pathway from **11** → **12** involves intramolecular alkylation followed by lactamization.

The formation of **7** and **12** from **10** and **11**, respectively, corresponds to intramolecular homoconjugate addition *via* what has been termed the spiro mode.[1] As in the case of the carbocyclic series, no products corresponding to the alternative fused mode of attack are observed when the spiro mode[1] gives five- or six-membered primary ring products. In this connection it was of interest to examine the chemistry of amino diester **14** which might, in principle, have given, as primary products, an azetidine *via* the spiro mode or a pyrrolidine through the fused mode. Both processes have precedent,[1] though under drastic conditions, in the carbocyclic series.[1] In practice, depthaloylation of **4** *via* hydrazinolysis in methanol at room temperature gives upon work-up the desired **14**[4a] (63%). Upon standing in neat form, **14** cyclizes to give lactam ester **15** mp 133–136°.[4] No evidence for intramolecular homoconjugate addition was observed in this instance. However, these results do not constitute a valid test of the feasibility of the ring opening reactions, since lactamization prevents their occurence.[8]

Further studies of heterocyclic synthesis *via* activated cyclopropanes are in progress as are adaptations of this scheme to the synthesis of related alkaloids.[2a]

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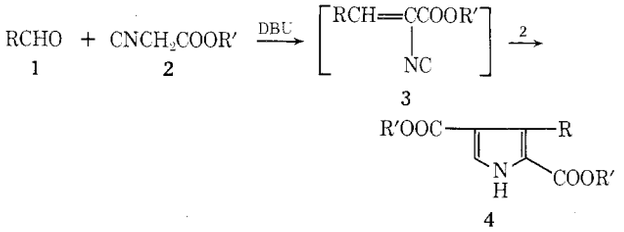
A Convenient Synthesis of 3-Substituted Pyrrole-2,4-dicarboxylic Acid Esters[1]

Summary: Pyrrole compounds **4** were synthesized by the reaction of isocyanoacetates with aldehydes in the presence of DBU in good yields.

Sir: In the course of our studies on the synthesis of amino acids and related compounds using isocyano compounds, we have investigated the reaction of isocyanoacetates **2** with aldehydes as a source of 3-substituted pyrrole-2,4-dicarboxylic acids. Schöllkopf, *et al.*, have detected diethyl 3-methylpyrrole-2,4-dicarboxylate from the reaction of acetaldehyde and ethyl isocyanoacetate in the presence of metallic base during the synthesis of ethyl α-formylaminoacrylate.[2]

We have carried out the condensation of alkyl isocyanoacetates with a variety of aliphatic and aromatic aldehydes in THF solution, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (Table I). Spectral and analytical data confirm the pyrrole structures **4**. The reaction does not require anhydrous conditions.

The reaction presumably involves Michael addition of isocyanoacetate **2** to the α-isocyanoacrylate **3**; **4** (R = H; R′ = CH_3) was obtained in 60% yield from the condensation of **2** and methyl α-isocyanocinnamate.[3] However, the pyrrole was not obtained from the reaction of methyl α-formamidocinnamate with **2**.



1 2 3 4

Typical Procedure. To a mixture of methyl isocyanoacetate (1.98 g, 0.02 mol) and DBU (3.0 g, 0.02 mol) dissolved in THF (30 ml) was added dropwise benzaldehyde (1.06 g, 0.01 mol) in THF (10 ml) at 45–50° for a period of 15 min with stirring. After stirring for 5 hr at same temperature, the reaction mixture was neutralized with acetic acid and then the solvent was removed under reduced pressure. The resulting residue was extracted with ethyl acetate and the extract was washed with hydrochloric aicd and water, dried, and then evaporated *in vacuo*. The crystals (1.3 g) recrystallized from aqueous methanol showed mp 183–185°. The mass spectrum of this compound showed the M^+ at *m/e* 259 and the ir spectrum (nujol) showed an NH band at 3370 cm^{-1} and two ester C=O bands at 1735 and 1700 cm^{-1}, respectively. The nmr spectrum ($CDCl_3$) indicated the presence of two ester groups (CH_3) [δ 3.58 (s) and 3.51 (s)], NH [12.04 (br)], pyrrole C-5 H [7.52 (d)], and aromatic H [7.25 (s)].

Table I
Preparation of Pyrrole Derivative 4

R	R′	Conditions: Temp, °C	Conditions: Hr	Mp, °C[a,b]	Yield, %
H	CH_3	50–55	1	125–126	67
CH_3	$(CH_3)_2CH$	50–55	1	74–76	71
CH_3CH_2	CH_3CH_2	45–50	1	87–89[c]	63
Ph	CH_3	45–50	5	183–185	50
4-Methoxy Ph	CH_3	55–60	4	146–147	57
3,4,5-Trimethoxy Ph	CH_3	10–15	2	189–192	59
3-Pyridine	CH_3	50–55	3	212–213	60
3-Indole	CH_3	50–55	3	>250	58

[a] Recrystallization from aqueous ethanol or methanol. [b] Analyses agreed with the calculated values within ±0.3%. [c] Lit. mp 88.5–89°: R. Grigg, A. W. Johnson, and T. W. F. Wasley, *J. Chem. Soc.*, 359 (1963).

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Melanin. I. Kinetics of the Oxidative Cyclization of Dopa to Dopachrome

Summary: Kinetics of the ring-closure of dopaquinone (**2**) to cyclodopa (**3**) have been studied *via* chronoamperometry of dopa (**1**) in the pH range of 5.0–6.0 and at temperatures of 15, 25, 30, and 37°; the rapidity of the cyclization process is attributed to a very favorable positive activation entropy; at pH 6.6 and above, cyclic voltammetry of dopa clearly demonstrates the formation of 5,6-dihydroxyindole (**5**).

Sir: Biogenesis of the important mammalian pigment melanin[1-4] from 3,4-dihydroxyphenylalanine (**1**, dopa) has long been considered to proceed *via* the series of fugitive intermediates illustrated in Scheme I, a pathway originally postulated by Raper[5] and not yet adequately characterized. Mason[6] has estimated the rate constant for decarboxylative rearrangement of dopachrome (**4**) to 5,6-dihy-