From a synthetic point of view methanolysis of **1** (and likely similar unimolecular solvolyses) appears to be of limited usefulness. Solvolysis of **1** and **2** in aprotic solvents in the presence of strong nucleophiles should conversely represent a good alternative to the displacement of analogous 21-chloro derivatives **1g**[2] and **2c**[5] for the introduction of substituents at C-21.

Experimental Section[6]

17α-Pregna-5,20-dien-3β,17-diol 3-Acetate 17-Trifluoroacetate (1). A solution of 17α-pregna-5,20-dien-3β,17-diol 3-acetate (**1a**)[2] (0.36 g, 1 mmol) in pyridine (1.7 mL) was treated with trifluoroacetic anhydride (0.7 mL) at 0 °C for 15 min. Then cold 1 N HCl (11.7 mL) was added and the mixture was extracted with ether. The ether layers were washed to neutrality with cold water, dried (Na_2SO_4), and evaporated. The residue (0.45 g) was crystallized from *n*-hexane (0.33 g): mp 118–119 °C; $[\alpha]_D$ −39°; IR (CF_3COO) 1770 cm^{-1}; ^1H NMR δ 0.95 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 5.13 (1 H, dd, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.33 (1 H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.37 (1 H, m, C-6H), 5.91 (1 H, dd, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz, C-20 H).[7] Anal. Calcd for $C_{25}H_{33}F_3O_4$ (454.5): C, 66.06; H, 7.32; F, 12.54. Found: C, 66.06; H, 7.32; F, 12.52.

Solvolysis of 1 in Methanol in the Presence of Sodium Acetate. A stirred solution of **1** (0.30 g, 0.66 mmol) and sodium acetate (0.11 g, 1.32 mmol) in 8 mL of methanol was heated at 60 °C for 4 h.[8] Methanol was then evaporated and the product was isolated with ether. The ethereal solution was washed twice with water and then dried (Na_2SO_4). The residue (0.25 g) was chromatographed on alumina (1.25 g). Elution with *n*-hexane–benzene (1:1) gave olefins (15 mg, 6%), followed by **17 α-methoxypregna-5,20-dien-3β-yl acetate (1b,** 23 mg, 9%): mp 137–138 °C (from methanol); $[\alpha]_D$ −83°; ^1H NMR δ 0.59 (3 H, s, 13-Me), 1.00 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 3.05 (3 H, s, 17α-OMe), 4.6 (1 H, m, 3α-H), 5.10 (1 H, dd, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.25 (1 H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.38 (1 H, m, C-6 H), 5.69 (1 H, dd, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz, C-20 H).[7] Anal. Calcd for $C_{24}H_{36}O_3$ (372.5): C, 77.37; H, 9.74. Found: C, 77.31; H, 9.77.

Elution with benzene gave first **(*E*)-21-methoxypregna-5,17(20)-dien-3β-yl acetate** (1c, 53 mg, 21%): mp 87.5–88.5 °C (from methanol); $[\alpha]_D$ −63°; ^1H NMR δ 0.77 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 3.30 (3 H, s, 21-OMe), 3.90 (2H, d, *J* = 7 Hz, CH_2OMe), 4.6 (1 H, m, 3α-H), 5.21 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.39 (1 H, m, C-6 H).[7] Anal. Calcd for $C_{24}H_{36}O_3$ (372.5): C, 77.37; H, 9.74. Found: C, 77.05; H, 9.75.

A second eluate with benzene gave the alcohol **1a** (22 mg, 9%).

Finally elution with benzene–ether (7:3) gave **(*E*)-pregna-5,17(20)-dien-3β,21-diol 3-acetate (1d,** 122 mg, 49%): mp 177–178 °C (from diisopropyl ether); $[\alpha]_D$ −61°; ^1H NMR δ 0.77 (3 H, s, 13-Me), 1.03 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.12 (2 H, d, *J* = 7 Hz, CH_2OH), 4.6 (1 H, m, 3α-H), 5.28 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.38 (1 H, m, C-6 H).[7] Anal. Calcd for $C_{23}H_{34}O_3$ (358.5): C, 77.05; H, 9.56. Found: C, 76.80; H, 9.55.

(*E*)-Pregna-5,17(20)-dien-3β,21-diol 3-Acetate 21-Trifluoroacetate (1f). This was prepared in the same manner as **1** from 21-alcohol **1d** and crystallized from *n*-hexane: mp 99–101 °C; $[\alpha]_D$ −49°; IR (CF_3COO) 1770 cm^{-1}; ^1H NMR δ 0.78 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 4.82 (2 H, d, *J* = 7 Hz, CH_2OCOCF_3), 5.27 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.39 (1 H, m, C-6H).[7] Anal. Calcd for $C_{25}H_{33}F_3O_4$ (454.5): C, 66.06; H, 7.32; F, 12.54. Found: C, 66.13; H, 7.48; F, 12.54.

Solvolysis of 21-trifluoroacetate 1f in methanol in the presence of sodium acetate under the same conditions as for **1** resulted, after 15 min,[8] in the formation of the 21-alcohol **1d** exclusively.

Solvolysis of 17β-Trifluoroacetate 1 in HMPT in the Presence of NaN_3. **1** (0.23 g, 0.5 mmol) and NaN_3 (0.32 g, 5 mmol) in 5 mL of HMPT were stirred at 60 °C for 5 h.[8] The mixture was poured into water and extracted with ether. The extract was washed with water to neutrality and dried (Na_2SO_4). The residue (0.19 g) was directly crystallized from *n*-hexane to afford 0.14 g (73%) of **(*E*)-21-azido-pregna-5,17(20)-dien-3β-yl acetate (1e):** mp 105–106 °C; $[\alpha]_D$ −56°; IR ($\overline{N_3}$) 2100 cm^{-1}; ^1H NMR δ 0.78 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 4.82 (2 H, d, CH_2N_3), 5.27 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 5.39 (1 H, m, C-6H).[7] Anal. Calcd for $C_{23}H_{33}N_3O_2$ (382.5): C, 72.02; H, 8.67; N, 10.96. Found: C, 72.03; H, 8.76; N, 10.81.

The only other components found in the mother liquors were a relatively nonpolar substance (7%)[4] and alcohol **1d** in traces.

In the same manner as above solvolysis of **1f** was carried out in HMPT + NaN_3 to give **1e** in 1 h[8] in 100% yield.

When **1** was heated in HMPT at 60 °C partial isomerization into **1f** occurred. NMR analysis showed a **1**:**1f** = 85:15 ratio after 1 h. The ratio went down to a 66:34 value in 3 h.

3-Methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-yl Trifluoroacetate (2). This was prepared in the same manner as **1** from 3-methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol (**2a**) and crystallized from *n*-hexane: mp 124 °C; $[\alpha]_D$ +72°; IR (CF_3COO) 1770 cm^{-1}; ^1H NMR δ 0.98 (3 H, s, 13-Me), 3.75 (3 H, s, 3-OMe), 5.17 (1 H, dd, J_{trans} = 17 Hz, J_{gem} = 1.5 Hz, C-21H), 5.37 (1 H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, C-21 H), 5.97 (1 H, dd, J_{trans} = 17 Hz, J_{cis} = 10.5 Hz, C-20 H), 6.62–7.23 ppm (3 H, aromatic protons).[7] Anal. Calcd for $C_{23}H_{27}F_3O_3$ (408.5): C, 67.63; H, 6.66; F, 13.95. Found: C, 68.27; H, 6.82; F, 13.96.

Solvolysis of 2 in HMPT in the presence of NaN_3 in the same conditions as for **1** gave 0.17 g of a residue (from 0.20 g of **2**) which was chromatographed on PLC [benzene–*n*-hexane (1:2) as eluant] to afford 0.14 g (82%) of **(*E*)-3-methoxy-21-azido-19-norpregna-1,3,5(10),17(20)-tetraene (2b)** as an oil, pure by NMR analysis: $[\alpha]_D$ +51° (*c* 4.0); IR (N_3) 2100 cm^{-1}; ^1H NMR δ 0.81 (3 H, s, 13-Me), 3.73 (2 H, d, *J* = 7 Hz, CH_2N_3), 3.74 (3 H, s, 3-OMe), 5.23 (1 H, tt, *J* = 7, 2 Hz, C-20 H), 6.62–7.27 (3 H, aromatic protons).[7] Anal. Calcd for $C_{21}H_{27}N_3O$ (337.5): C, 74.74; H, 8.07; N, 12.45. Found: C, 74.58; H, 8.06; N, 12.27.

Registry No.—**1,** 65733-41-7; **1a,** 32782-36-8; **1b,** 65733-42-8; **1c,** 65733-43-9; **1d,** 65733-44-0; **1e,** 65733-45-1; **1f,** 65733-46-2; **2,** 65760-05-6; **2a,** 6885-48-9; **2b,** 65733-47-3.

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(7) A convenient illustration of the features of systems of the type >CCH═CH_2 and >C═$CHCH_2X$ is found in: N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy to Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, pp 85 and 112.
(8) The disappearance of starting material was monitored by TLC.

Photochemical Reduction and Decarboxylation of 2-Phenylquinoline-4-carboxylic Acids

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Though a variety of 2-phenylquinoline-4-carboxylic acids (cinchophens) and their derivatives have medicinal value,[2] some members of the family have been observed by Rothe[3] to cause phototoxicity in mice. We have previously found[5] that the phototoxicity of similar quinolinemethanol antimalarial compounds correlates with a surprisingly efficient photochemical fragmentation process. We have now studied five of the cinchophens and have discovered that, like the quinolinemethanols, these compounds also show unexpected photochemical reactivity.

Acids **1a–e** were prepared via Doebner condensations of the suitably substituted aniline and aldehyde. Irradiation led to

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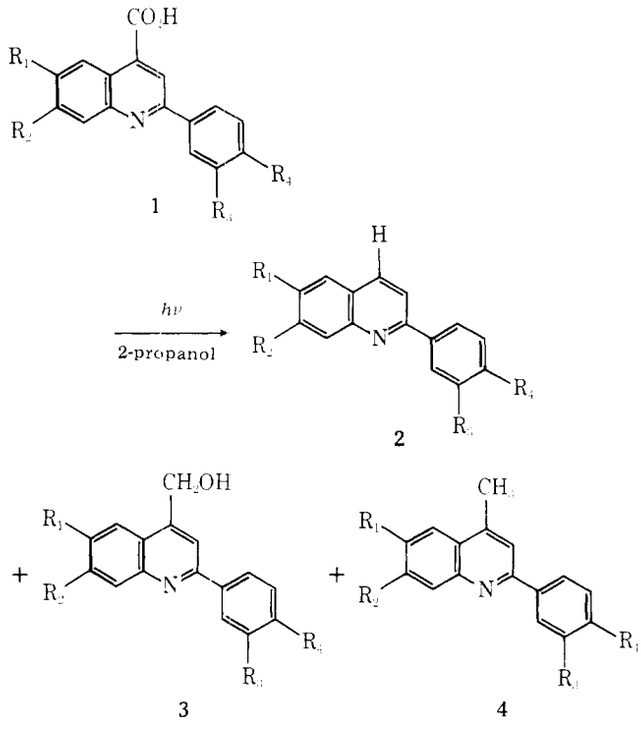
Table I. Isolated Products from Cinchophen Photolyses

compd no.	registry no.	isolated yield, % 2	registry no.	3	registry no.	4	registry no.
1a	19021-20-6	93	61576-11-2	1[a]	61576-10-1	6	66324-17-2
1b	19209-49-5	71	66373-83-9	*b*		5	66324-18-3
1c	20843-19-0	51	66324-15-0	*b*		4	66324-19-4
1d	32795-58-7	66	4789-73-5	2	66324-16-1	*b*	
1e	60538-98-9	86	27356-46-3	*b*		*b*	

[a] Observed only at low conversion. [b] Not detected; estimated yield <1%.



a, $R_1 = R_2 = CH_3O$; $R_2 = Cl$; $R_3 = H$
b, $R_1 = CH_3O$; $R_2 = H$; $R_3 = R_4 = Cl$
c, $R_1 = R_3 = H$; $R_2 = R_4 = F$
d, $R_1 = CH_3O$; $R_2 = R_3 = R_4 = H$
e, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$

photochemical decarboxylation and photoreduction. In all cases the decarboxylation pathway predominated, leading to **2** as the major product. Concurrently, about 5% of **3** or **4** was formed. Generally the products were isolated by silica gel chromatography; Table I summarizes the results obtained from photolysis of each compound.

Identification of products was based upon spectral analysis and independent synthesis. In each case protio compound **2** could be obtained by a thermal decarboxylation of the corresponding acid (**1**). The methanol derivates, **3**, were obtained by reduction of the methyl esters of **1a–e** with lithium aluminum hydride. The methyl compounds, **4**, were prepared by photochemical reduction of alcohol **3**[6] or by hydrogenolysis of the α-chloromethyl compound.

Both the photoreduction and decarboxylation of **1** were surprising, since there are few reports of such photochemical transformations of analogous compounds. The photochemical decarboxylation of arylcarboxylic acids is rare in solution, for reasons which are not entirely clear. Several reports[7] suggest that the preferred pathway of photochemical decarboxylation is via a homolytic fission to produce a radical intermediate. Such a fission would be expected to be more difficult with the carboxyl group directly attached to an aromatic ring, and a slower reaction would not be surprising. Evidence for this argument is found in Takeuchi's observation[8] that the photochemical decarboxylation of nicotinic acid proceeds preferentially from the anionic (ionized) form of the acid. Similarly, Cantrell[9] and Azuma[10] report the reluctance of benzoic acid and monosubstituted pyridine carboxylic acids, respectively, to photochemically decarboxylate in solution. In contrast to the behavior of nicotinic acid,[8] the decarboxylation of **1** does not proceed through an ionic mechanism, since photolysis of **1a** in basic solution retarded the rate of reaction about 50-fold. Further, photolysis in $(CH_3)_2CDOH$ led to incorporation of deuterium in the 4 position of the protio product, suggesting that a hydrogen atom is abstracted in one step of the mechanism, rather than a proton. Whether the reaction proceeds by a direct α cleavage or by an initial reduction of the quinoline ring cannot be determined at this point, however.

The formation of the minor product, **3** or **4**, was most surprising, since it is clearly formed by an unusual pathway. The intermediacy of alcohol **3** in the formation of **4** is probable, since irradiation of **3** under identical conditions leads almost exclusively to formation of the methyl compound. Further, the proportion of **3** is dependent upon extent of photolysis, ordinarily being totally absent at high conversions.

$$1 \xrightarrow{h\nu} \underset{?}{3} \xrightarrow{h\nu} 4$$

We have not yet determined whether the conversion of **1** to **3** proceeds by a direct photochemical reduction or by a "chemical sensitization" pathway in which a free radical produced from a different reaction transfers a hydrogen atom to *ground* state **1**.

The conversion of **1a** to **2a** and **4a** could be sensitized with both xanthone and Michler's ketone, and the conversion of **1b** to **2b** and **4b** was successfully sensitized with Michler's ketone, suggesting that the reactive excited state for the cinchophens is the triplet. Although the presence of cyclohexadiene did not affect the reaction of **1a**, the reaction was totally quenched by photolysis in the presence of oxygen, consistent with the assignment of the triplet as the reactive excited state. The proportion of products was independent of the presence of sensitizer or quencher.

We are continuing to investigate the mechanism and generality of the photochemical reactions of quinolinecarboxylic acids.

Experimental Section[11]

Preparation of the Cinchophens (1a–e). All cinchophens were prepared via a Doebner condensation of suitably substituted anilines and benzaldehydes with pyruvic acid.[12]

Irradiation Procedure. Irradiation of 1.0 g (2.9 mmol) of **1a** in 500 mL of 2-propanol for 2 h with a Hanovia 450 W mercury lamp, using a vycor filter, and purging with nitrogen throughout the photolysis was a typical reaction. The photolysate was concentrated in vacuo and separated by extraction into 0.23 g of an acidic fraction (unreacted **1a**) and 0.67 g of a neutral fraction (a mixture of **2a** and **4a**). The photoproducts were isolated by column chromatography of the neutral fraction using silica gel as an adsorbent and eluting with benzene. The results of this isolation procedure are summarized in Table I. The identity of the photoproducts was confirmed by comparison of their

spectral properties and TLC behavior with those of authentic samples prepared as described below.

Thermal Decarboxylation of the Cinchophens. Preparation of Protio Compounds 2a–e. Typically, a 1.0-g sample (2.9 mmol) of **1a** was melted by placing a test tube containing the sample blanketed with nitrogen into a Wood's metal bath at 275 °C for 4 min. Chromatography of the reaction product (silica gel, benzene eluent) gave 0.25 g (29%) of **2a** as the only mobile spot on TLC with benzene as an eluent. Recrystallized (benzene) constant-melting samples gave: **2a,** mp 189–190 °C; **2b,** mp 152–153 °C; **2c,** mp 95–97 °C; **2d,** mp 129–130 °C;[13] **2e,** mp 67 °C.[14]

Preparation of Alcohols 3a–d. Typically, 2.1 g (5.9 mmol) of the methyl ester of acid **1a** was treated with 0.250 g (6.6 mmol) of lithium aluminum hydride in ether. The usual workup gave 1.56 g (80%) of alcohol **3a,** mp 203–205 °C. Similarly, reduction of the methyl ester of **1b** gave **3b,** mp 188–189 °C, reduction of the methyl ester of **1c** gave **3c,** mp 195–196.5 °C, and **1d** led to **3d,** mp 138.5–139.5 °C.

Preparation of the 4-Methyl Derivatives 4a–c. Procedure A: A solution of 0.500 g (1.85 mmol) of alcohol **3c** in 10 mL of chloroform was treated with 0.500 g (2.40 mmol) of phosphorus pentachloride for 24 h. The crude α-chloro compound was subjected to hydrogenolysis using 50 mg of platinum oxide as a catalyst, ethanol solvent, and hydrogen at 45 psi for 1 h. Chromatography of the isolated product (1:1 hexane–benzene, silica gel) gave 0.180 g (38%) of **4c,** mp 95–97 °C. Procedure B: The direct photolysis of alcohols **3a** and **3b** in 2-propanol under nitrogen using a Hanovia 450 W mercury lamp and a Pyrex filter gave respectively **4a,** mp 148–150 °C, and **4b,** mp 130–131 °C. Characteristically, these 4-methyl compounds showed an NMR absorption at δ 2.6–2.7 as a singlet integrating for three protons.

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Registry No.—**3b,** 66324-20-7; **3c,** 66324-21-8.

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Convenient New Procedures for the Synthesis of Ethoxythiocarbonyl Derivatives of Amino Acids[1a]

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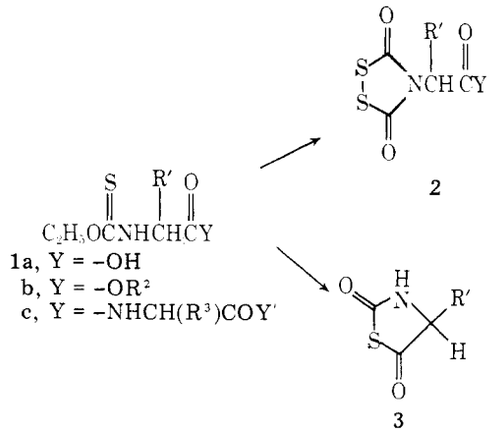
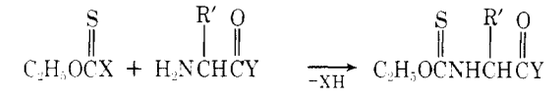
Ethoxythiocarbonyl (Etc) derivatives of amino acids **1a** and their esters **1b** are synthetic precursors to the thiol-labile dithiasuccinoyl (Dts) N^{α}-amino protecting group[2] recently developed for peptide synthesis (**2** in Scheme I). They are also intermediates in the preparation of *N*-thiocarboxy anhydrides **3** of α-amino acids (1,3-thiazolidine-2,5-diones),[3a,b] which were reported to have certain advantages for peptide synthesis[4,5] by comparison to their oxygen analogues, *N*-carboxy anhydrides. Etc derivatives **1a** and **1c** have also been explored for use as reversible amino protecting groups[6] and in a scheme for stepwise degradation of peptides,[7,8] but these applications appear to be of limited scope.

Scheme I. Synthetic Applications of Ethoxythiocarbonyl (Etc) Amino Acids and Derivatives



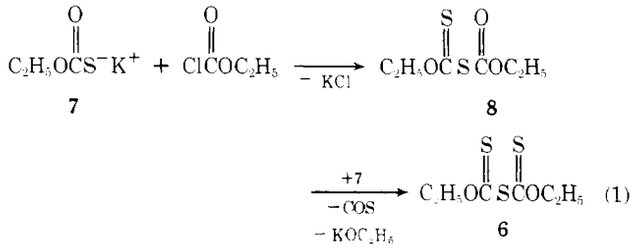
Scheme II. Synthesis of Ethoxythiocarbonyl (Etc) Derivatives of Amino Acids



4, X = -Cl
5, X = $-SCH_3$
6, X = $-SCSOC_2H_5$
10, X = $-SCH_2CO_2H$

Etc derivatives of amino acids can in principle be prepared with one of the following known reagents: ethoxythiocarbonyl chloride (**4**),[9–11] *O*-ethyl *S*-methyl dithiocarbonate (**5**),[12,13] or bis(ethoxythiocarbonyl) sulfide (**6**)[14–17] (Scheme II). Compound **4** is difficult to prepare and handle.[18] Compound **5,** while allowing formation of Etc derivatives in high yields under alkaline conditions,[4,7,8,19] is unattractive due to the stench of the methanethiol evolved in the reaction. Compound **6** does not have the disadvantages of compounds **4** and **5.** We found that it is easy to prepare and that it reacts rapidly with amino acids in aqueous solutions at pH 8–10 to give the desired derivatives in nearly quantitative yields after a straightforward workup. Progress of the reaction can be followed titrimetrically (an equivalent of base is consumed) or spectrophotometrically (Etc derivatives of amino acids have λ_{max} 245 nm with ϵ 1.3–1.5 × 10^4).

Compound **6** was originally isolated as a by-product from the synthesis of diethyl thionothiodiformate (**8**) on reaction of equimolar amounts of potassium ethyl xanthate (**7**) and ethyl chloroformate (eq 1).[14,20] We found that compound **6** can be easily obtained as the main product in place of compound **8** when the molar ratio of ethyl chloroformate to ethyl



(1)

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