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Preparation of Anhydrous *N*,*N'*-Dicyclohexylalloxan and Its Use in Dehydration

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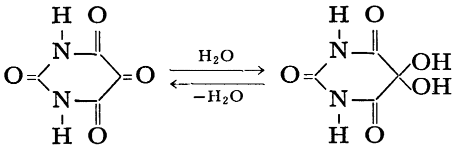
Synopsis. Anhydrous *N*,*N'*-dicyclohexylalloxan has been prepared and used as a dehydrating agent for carboxylic acids in the esterification of carboxylic acids with alcohols.

Alloxan(A), a vicinal carbonyl compound (reducton), is known to play an important role in biological oxidation-reduction systems in the same way as ascorbic acid. The central carbonyl, activated by the two adjacent carbonyl groups, is reactive such that it readily combines with one mole of water to form the hydrate (A-hydrate).[1] The photochemical reactions of the A-hydrate have been reported.[2,3]

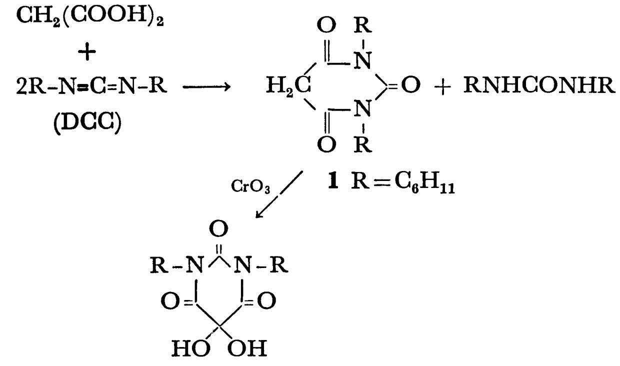


(A) (A-hydrate)

The study of alloxan has been extended especially in the redox system mediated by the alloxan radical produced photochemically or chemically from the A-hydrate.[4,5]

This paper describes the synthesis of anhydrous *N*,*N'*-dicyclohexylalloxan and the use of the hydrate in the esterification of carboxylic acids with alcohols.

A and A-hydrate are soluble in water and alcohols, but insoluble in common organic solvents. The preparation of *N*,*N'*-dialkylalloxan was directed to achieving soluble alloxan in general organic solvents. Alloxans may be prepared by oxidation of the corresponding barbituric acids, which are obtained from diethyl malonate and ureas, using chromium trioxide.[6] *N*,*N'*-Dicyclohexyl barbituric acid(**1**) was prepared by the reaction of malonic acid and dicyclohexylcarbodiimide (DCC).[7] *N*,*N'*-Dicyclohexylalloxan (**2**) as the hydrate was obtained by the oxidation of **1** with chromium trioxide at room temperature in a mixture of acetic acid and water, and identified by IR and elemental analyses.



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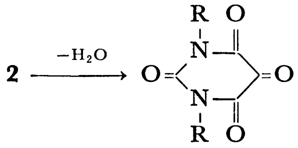
Anhydrous alloxan was prepared by heating alloxan hydrate *in vacuo* (4 mmHg†) at 150 °C.[8] Anhydrous *N*,*N'*-dicyclohexylalloxan was prepared by 1) heating the hydrate at reduced pressure (170—180 °C/1 mmHg), 2) treatment with acetic anhydride at 80 °C or 3) treatment with DCC at room temperature. Synthetically method 1 is the most convenient, since for methods 2 and 3 a process is needed to separate **3** from the reaction mixture. In the IR spectrum of **3** the OH group absorption (3450 cm^{-1}) disappeared completely and was accompanied by the appearance of a new absorption band of the C–O group at 1760 cm^{-1}.



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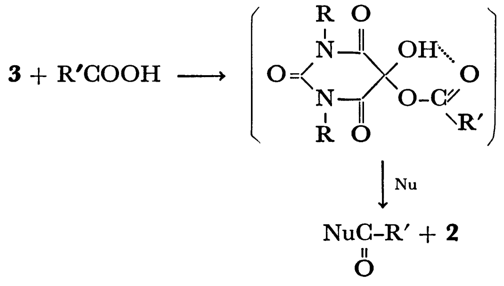
Compound **3** thus obtained was examined in terms of its suitability as a dehydrating agent. Anhydrous alloxan (A) is not suitable as a dehydrating agent because of possible side reactions. Acetic acid was treated with equimolar quantities of **3** in tetrahydrofuran (THF) at room temperature to give quantitatively acetic anhydride together with **2**. The esterification of carboxylic acids with alcohols using **3** was conducted in THF at room temperature. The corresponding esters were obtained in reasonable yields as shown in Table 1. In the condensation of carboxylic acids and amines the same method is impossible to use since **3** reacts preferentially with amines.[9] The reaction may proceed *via* an activated intermediate of the carboxylic acid as shown below:



Nu; R''OH, R''COOH

Several anhydrous inorganic salts (*e.g.* Na_2SO_4, $MgSO_4$) have been used as dehydrants. **3** is novel example of a dehydrating agent for ester formation which can be reproduced by heating **2** and can be used repeatedly.

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† 1 mmHg=133.322 Pa.

Table 1. Esterification of carboxylic acids with alcohols by anhydrous *N*,*N*-dicyclohexylloxan (**3**)

Carboxylic acid (R′)	Alcohol (R″)	Yield of isolated ester (%)
CH_3	CH_3CH_2	55
CH_3	$CH_2C_6H_5$	60
CH_3	$C_{12}H_{25}$	53
C_6H_5	CH_3CH_2	40

Experimental

The synthesis of *N*,*N*′-dicyclohexylbarbituric acid(**1**) (mp 207—208 °C) was prepared from DCC and malonic acid.[7]

Preparation of N,N′*-Dicyclohexylalloxan (**2**).* To a solution of chromium trioxide (15 mmol) in a mixture of water–acetic acid (15 ml) (1/4, v/v) was added a solution of **1** (10 mmol) at 30 °C. After stirring for 2 h at 25—30 °C, the reaction mixture was poured into water and then the precipitate filtered and dried under vacuum. The alloxan was recrystallized from carbon tetrachloride. Yield; 90%, mp 212—214 °C. IR (KBr, cm^{-1}): 3370 (ν_{OH}); 1690 (ν_{CO}). Found: C, 59.20; H, 7.47; N, 8.62%. Calcd for $C_{16}H_{24}O_5N_2$: C, 59.24; H, 7.46; N, 8.64%.

Preparation of Anhydrous N,N′*-Dicyclohexylalloxan (**3**).* **3** was synthesized by three methods: 1) **3** was sublimated by heating **2** at 170—180 °C/1 mmHg for 15 h (97% yield). 2) A solution of **2** (10 mmol) in acetic anhydride (30 ml) was heated at 80 °C for 5 h. After the excess acetic anhydride was removed under vacuum, the residue was recrystallized from carbon tetrachloride to give **3** (90% yield). 3) To a solution of **2** (10 mmol) in THF (30 ml), DCC (10 mmol) was added at room temperature and the reaction mixture stirred at 40 °C for 7 h. The *N*,*N*′-dicyclohexylurea was filtered and the THF evaporated under vacuum. The residue was recrystallized from carbon tetrachloride to give **3**′ (85 yield). Mp 229—231 °C. IR (KBr, cm^{-1}): 1760, 1710, 1690 (ν_{CO}). UV (THF, nm): 420, 257 (λ_{max}). Found: C, 62.70; H, 7.59; N, 9.45%. Calcd for $C_{16}H_{22}O_4N_2$: C, 62.75; H, 7.52; N, 9.48%.

*Reaction of **3** with Acetic Acid.* To a solution of **3** (30 mmol) in THF (30 ml) was added acetic acid (33 mmol) at room temperature and the reaction mixture was stirred at room temperature for 7 h. The THF was removed and the residue was distilled to give acetic anhydride quantitatively and **2** was recovered from the residue.

*Esterification of Carboxylic Acids with Alcohols by the Use of **3**.* To a solution of **3** (10 mmol) in THF (30 ml) was added the carboxylic acid at room temperature; alcohol (11 mmol) was then added to the reaction mixture. After the mixture was stirred at room temperature for 10 h, the THF was evaporated. The obtained residue was distilled to give the corresponding ester as shown in Table 1, and **2** was obtained quantitatively from the residue after distillation.

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