After heating at 100° for 3–4 hr the salt was dissolved in cold H_2O and washed with Et_2O when **55** (7.5 g) sepd as yellow prisms. It was crystd from EtOH, mp 137–138°. *Anal.* ($C_{16}H_{17}NO_6$) C, H, N.

Similarly, condensation of diethyl *N*-*o*-tolyldiglycolamidate (3 g) and diethyl oxalate (1.85 g) gave **56** (1 g) on acidification of the soln of the Na salt. It was crystd from EtOH, mp 140–141°. *Anal.* ($C_{17}H_{19}NO_6$) C, H.

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Preparation of Some Trimethylpentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8,11-dione Derivatives

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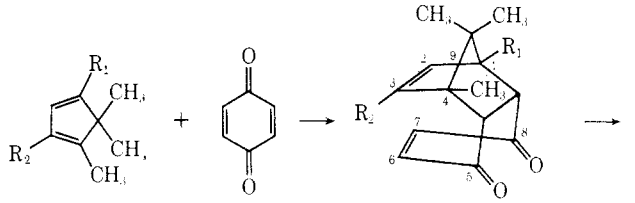
The prophylactic use of 1-aminoadamantane against Asian influenza in man has been described.[1] It appeared interesting to determine what other "cage" systems might combine a desirable size and shape with an unsubstituted amino function to produce structures having antiinfluenzal activity. The preparation of derivatives of the birdcage hydrocarbon,[2] homocubane[3] and noradamantane,[4] has already been reported from these laboratories. We now wish to report the preparation of amino derivatives of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione.

This cage system ($R_1 = R_2 = H$) was first prepared by Cookson and coworkers by the photocyclization of the Diels–Alder adduct of *p*-benzoquinone and cyclopentadiene.[5] In the present study, access to the cage system with an amino function was accomplished by using cyclopentadienes having a carboxyl group at the appropriate position in a reaction sequence paralleling that described by Cookson, *et al.* The resulting cage acid was converted to the amine in the last step.

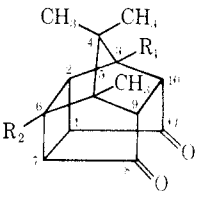
To obtain the 3-amino derivative of this system, the Me ester of α-camphylic acid[6] was condensed with *p*-benzoquinone to give the endo adduct **2a** which, upon uv irradiation in acetone, closed to the saturated diketone **3a**. Hydrolysis of **3a** with 48% HBr gave the free carboxylic acid **3b** which was converted to the amine **4a** *via* a modified Curtius reaction.[7]

Similarly, β-camphylic acid (**1b**)[6] was condensed with *p*-benzoquinone to give adduct **2b**. Irradiation of **2b** gave the cage acid **3c** which was characterized as the Et ester **3d**. This (**3c**) was converted, *via* the modified Curtius reaction, to the amine **4b**. The possibility that photolysis of **2a** and **2b** had resulted in dimerization[8] rather than intramolecular cyclization was ruled out by



1a, $R_1 = COOCH_3$; $R_2 = H$
1b, $R_1 = H$; $R_2 = COOH$

2a, $R_1 = COOCH_3$; $R_2 = H$
2b, $R_1 = H$; $R_2 = COOH$



3a, $R_1 = COOCH_3$; $R_2 = H$
3b, $R_1 = COOH$; $R_2 = H$
3c, $R_1 = H$; $R_2 = COOH$
3d, $R_1 = H$; $R_2 = COOC_2H_5$
4a, $R_1 = NH_2$; $R_2 = H$
4b, $R_1 = H$; $R_2 = NH_2$

determining the molecular weights (mass spectra) of the condensation products **3a** and **3c**.

Biological Activity.—The cage amines and several of the intermediates described were tested *in vitro* (plaque inhibition)[9] for antiinfluenza activity. The amines were also tested for activity against influenzal pneumonitis in mice.[10] Compds **2b, 4a,** and **4b** showed no activity *in vitro* against influenza A (WSN), parainfluenza 1 (Sendai), and influenza A_2 (Ann Arbor), but **3a** and **3c** had marginal activity against influenza A (WSN). Compd **4a** showed marginal activity against influenzal pneumonitis [influenza A_2 (Ann Arbor), well-tolerated dose in mice, 100 mg/kg; increase in per cent survival, 10%; increase in mean survival days, 1.4 days]. Compd **4b** was inactive against both influenza A_2 (Ann Arbor) and A_1 (swine) in mice.

Experimental Section

General.—Irradiation was carried out with a 250-W Hanovia medium-pressure Hg lamp in Pyrex apparatus. All mp (Thomas-Hoover apparatus) and bp are uncorrected.

Methyl 1,4,4a,5,8,8a-Hexahydro-4,9,9-trimethyl-5,8-dioxo-1,4-methanonaphthalene-1-carboxylate (2a).—Attempts to condense α-camphylic acid with *p*-benzoquinone returned only unreacted starting material. Consequently, the condensation was carried out using the Me ester. Methyl α-camphylate was prepd in 85% yield by methylation of α-camphylic acid[11] with CH_2N_2. A soln of 10.8 g (64 mmoles) of methyl α-camphylate and 7.0 g (64 mmoles) of recrystd *p*-benzoquinone in 130 ml of C_6H_6 was refluxed in the dark under N_2 for 22 hr. Upon removal of C_6H_6 *in vacuo*, the residual oil solidified. The crude product was crystd from aq MeOH to give 9.48 g (54%) of a yellow solid: mp 110–112°; nmr ($CDCl_3$), 0.82 (3 H, s), 1.02 (3 H, s), and 1.35 (3 H, s), CH_3 groups, 3.22 and 3.95 (2 H as AB quartet, J = 9 Hz), $C_{4a}H$ and $C_{8a}H$, 3.87 (1 H, s) OCH_3, 5.84 and 6.23 (2 H as AB quartet, J = 6 Hz), C_2H and C_3H, 6.63 (2 H, s) C_6H and C_7H. *Anal.* ($C_{16}H_{18}O_4$) C, H.

4,4,5-Trimethyl-8,11-dioxopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-3-carboxylic Acid (3b).—A soln of 1.9 g (6.94 mmoles) of adduct **2a** in 450 ml of EtOAc was irradiated for 24 hr under N_2. The colorless soln was concd *in vacuo* to a small vol to give

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(10) R. Stewart, "Methods in Drug Evaluation," P. Mantegazza and F. Piccinini, Ed., North-Holland Publishing Co., Amsterdam, 1966, p 379.
(11) α-Camphylic acid can also be prepd from the β isomer by heating the latter at 175° for 15 hr in a closed system.

1.2 g (63%) of ester **3a** as a white solid. A sample was recrystd from EtOAc–petr ether for anal.: mp 121–123°; ir, 5.65 (CO), 5.75 μ ($COOCH_3$). The conjugated double bond peak at 6.2 μ, present in the starting material, had disappeared upon closure to the cage system: nmr ($CDCl_3$), 0.95 (6 H, s), C_{11} $(CH_3)_2$, 1.05 (3 H, s), C_8CH_3, 2.5–3.2 (6 H, m), $(CH)_6$, 3.71 (3 H, s), OCH_3; glc (column temp 250°), one peak; mol wt, mass spectrum *m/e* 274, calcd for $C_{16}H_{18}O_4$ 274.3. *Anal.* ($C_{16}H_{18}O_4$) C, H. The hydrolysis was carried out by heating 11.0 g (40 mmoles) of ester **3a** in 95 ml of 48% HBr on a steam bath for 0.5 hr. The amber-colored soln was poured into 150 g of ice, and acid **3b** sepd as a white solid (7.5 g, 72%). Recrystn from EtOAc–petr ether gave an anal. sample: mp 228–230°; ir 2.98 broad (OH), 5.78 (CO), and 5.85 μ (COOH); uv, λ_{max} 286 (ε 37). After drying at 160°, *in vacuo*, *Anal.* ($C_{15}H_{16}O_4$) C, H.

3-Amino-4,4,5-trimethylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione·HCl (4a).—The usual Curtius procedure was modified since the isocyanate which formed in the reaction could not be efficiently hydrolyzed with refluxing HCl in toluene or with HCl in THF. Acid **3b** (1 g, 3.6 mmoles) was added to 5 ml of $SOCl_2$. After spontaneous reaction at room temp, the soln was heated on a steam bath for 45 min. Excess $SOCl_2$ was removed *in vacuo*, and the residue was dissolved in 7 ml of Me_2CO. A soln of 4.5 g (69 mmoles) of NaN_3 in 2.5 ml of H_2O was added dropwise to the acid chloride–Me_2CO soln at −5°. After being stirred for 15 min, the mixt was poured on ice and extd with toluene (ir spectrum of the crude product showed the azide peak at 4.7 μ). The dried PhMe soln of the azide was heated on a steam bath with 45 ml of F_3CCO_2H and 7 ml of H_2O for 45 min and then evapd to dryness. The residue, which crystd, was triturated with THF to give 0.48 g (38%) of the amine as the trifluoroacetate salt.

A soln of 1.9 g (5.5 mmoles) of the amine trifluoroacetate was dissolved in hot H_2O and the pH was adjusted to 11 with 5% NaOH. Extn with $CHCl_3$ gave 0.9 g (75%) of the crude amine, which was converted *via* ethereal HCl to the amine·HCl **4a** (0.9 g, 65%). Purification was carried out by converting the crude hydrochloride to the free amine and repptg it as the HCl salt, mp 250° dec. This amine shows a great tendency to hydrate. Anhyd material could not be prepd by drying at 77° *in vacuo*. Finally the sample was equilibrated in air at room temp prior to anal.: ir, 3.00 (OH) and 5.71 μ (CO); nmr, (D_2O–DCl) 0.90 (6 H, s), $(CH_3)_2$, 1.07 (3 H, s), C_8–CH_3, 2.5–3.4 (6 H, m), $(CH)_6$. *Anal.* ($C_{14}H_{18}ClNO_2 \cdot H_2O$) C, H, Cl, N.

1,4a,5,8,8a-Hexahydro-1,9,9-trimethyl-5,8-dioxo-1,4-methanonaphthalene-2-carboxylic Acid (2b).—A soln of 10.0 g (65 mmoles) of β-camphylic acid (**1b**) and 6.5 g (61 mmoles) of recrystd *p*-benzoquinone in 110 ml of C_6H_6 was allowed to react according to the procedure for **2a** to give 9.5 g (68%) of **2b**, mp 207–209° dec. An anal. sample was prepd by recrystn from EtOAc–petr ether (charcoal): mp 207.5–209° dec; nmr (CF_3COOH), 1.00 (3 H, s), 1.10 (3 H, s), 1.58 (3 H, s), CH_3 groups, 3.33–3.60 (2 H, m), C_{4a} and C_{8a}(CH), 3.8–4.1 (1 H, m), C_4H, 6.96 (2 H, s), C_6 and C_7 (CH), 7.37 (1 H, d), C_3H. *Anal.* ($C_{15}H_{16}O_4$) C, H.

3,4,4-Trimethyl-8,11-dioxopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-2-carboxylic Acid (3c).—A soln of 2.0 g (7.6 mmoles) of the β-camphylic acid–*p*-benzoquinone adduct **2b** and 450 ml of EtOAc was irradiated according to the procedure for **3b** to give 2.0 g of cage acid **3c** as a white solid. In contrast to α-camphylic acid, the β isomer readily condensed with *p*-benzoquinone as the free acid. A sample was sublimed at 175° (0.05 mm). It did not melt or decompose at 250°. Upon exposure to air, the acid was partially hydrated: ir, 2.97 μ and 3.06 (OH), 5.70 (CO), 5.90 μ (COOH). The anhyd product was obtd by drying at 77° *in vacuo* over P_2O_5: ir, at 5.65, 5.75 (CO), and 5.88 μ (COOH). The ease of hydration in this type of cage system has also been observed by Cookson and coworkers:[12] nmr ($CDCl_3$), 1.04 (6 H, s), C_{11} $(CH_3)_2$, 1.12 (3 H, s) C_8–CH_3, 2.0–4.0 (6 H, m) $(CH)_6$, 9.72, COOH; mol wt, mass spectrum *m/e* 260, calcd for $C_{15}H_{16}O_4$, 260.3.

Because this acid hydrates readily, it could not be analyzed satisfactorily. Instead, it was characterized as its Et ester which appeared to be less prone to hydration. In this case, a soln of 0.52 g (2 mmoles) of acid **3c** in 9 ml of THF was cooled to 0°, and 0.4 ml (3.9 mmoles) of Et_3N was added dropwise, followed by 0.22 g (2 mmoles) of ethyl chloroformate. This reaction mixt was stirred 15 min at 0° and filtered. EtOH (0.1 ml, 0.09 g) was added to the filtrate, and this mixt was stirred at room temp for 45 min. It was concd to an oil which, upon trituration with EtOAc–petr ether, gave **3d** as a white solid. Recrystn from the same solvent (charcoal) gave an anal. sample, 257.5–259.5°. *Anal.* ($C_{17}H_{20}O_4$) C, H.

2-Amino-3,4,4-trimethylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8,11-dione·HCl (4b).—A soln of 11.8 g (45 mmoles) of acid **3c** in 40 ml of THF was cooled to 0–5°, and 4.6 g (46 mmoles) of Et_3N was added dropwise with stirring followed by 4.8 g (46 mmoles) of ethyl chloroformate and 6.0 g (92 mmoles) of NaN_3 in 16 ml of H_2O. The mixt was worked up according to the procedure for **4a** to a brown oil which crystd on standing. Recrystn from EtOAc–petr ether gave 6.5 g (40%) of purified amine **4b** as the trifluoroacetate, mp 153–155°. The free amine is water sol and could not be extd by organic solvents. Consequently, an aq soln of the trifluoroacetate was stirred with a strong base anion-exchange resin (Rexyn 201-OH) and then evapd to give the free amine as an oily solid. The amine was converted to its solid HCl salt with ethereal HCl. Recrystn from *i*-PrOH–petr ether gave 1.8 g (15.0%) of the purified amine·HCl, mp 206–209° dec. Glc (column temp 250°) of the free amine gave one peak. Tlc of the amine·HCl (silica gel, MeOH–C_6H_6, 3:1, and contg a drop of ethereal HCl) showed only 1 spot: ir, 2.85 and 2.90 (NH), 5.65 and 5.80 μ (CO); nmr (D_2O–DCl), 0.95 (3 H, s) CH_3, 1.13 (6 H, s) $(CH_3)_2$, 2.2–3.2 (6 H, m) $(CH)_6$. *Anal.* ($C_{14}H_{18}ClNO_2$) C, H, Cl, N.

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