Adriamycin Analogues. Preparation of 9,10-Anhydrodaunorubicin, 9,10-Anhydroadriamycin, and Some Related Compounds

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The title compounds, as well as 9,10-anhydro-*N*-(trifluoroacetyl)adriamycin 14-valerate (9,10-anhydro-AD 32), were prepared starting from daunorubicin, adriamycin, and *N*-(trifluoroacetyl)adriamycin 14-valerate (AD 32), respectively. In addition, 9-deoxydaunorubicin and 9-deoxy-AD 32 were obtained by catalytic hydrogenation of the appropriate olefin. All of the products were significantly less active than the parent drugs in inhibiting the growth of CCRF-CEM (human lymphoblastic leukemic) cells in culture. The results suggest the importance of the tertiary alcohol function, as found in the parent compounds at the anthracycline 9 position, in contributing to the expression of biological activity of these agents.

Previous studies in these laboratories have led to the preclinical development and clinical introduction of the semisynthetic adriamycin analogue *N*-(trifluoroacetyl)-adriamycin 14-valerate (AD 32).[1-8] The parent antibiotic adriamycin and the close structurally related fermentation products daunorubicin and carminomycin are generally thought to exert their antitumor action via DNA intercalation.[9] *N*-(Trifluoroacetyl)adriamycin 14-valerate, however, does not bind to double-helical DNA,[10] and the therapeutic superiority of this analogue over adriamycin in experimental animal tumor systems thus becomes remarkable and raises significant questions about the validity of the DNA-binding hypothesis. One approach to gaining further insight into the possible mechanism(s) of action of these compounds is through analysis of structure–activity relationships. In connection with such studies here, we recently investigated the synthesis and biological properties of a selected number of *N*-(perfluoroacyl)-anthracycline derivatives. During this investigation, it was observed that daunorubicin, adriamycin, and their derivatives when treated with a perfluoroacyl anhydride in pyridine at room temperature give 9,10-anhydro products, with concommitant N-perfluoroacylation if the glycosidic amino function is otherwise unsubstituted.[11] From appropriate dehydrated *N*-acylanthracycline materials we have now prepared 9,10-anhydrodaunorubicin (**2**), 9,10-anhydroadriamycin (**9**), 9-deoxydaunorubicin (**5**), and 9-deoxy-*N*-(trifluoroacetyl)adriamycin 14-valerate (9-deoxy-AD 32; **12**) and have examined these agents, relative to their parent drugs, for growth-inhibitory activity against human leukemic cells in culture.[12]

The preparation of the daunorubicin-related compounds is shown in Scheme I. Daunorubicin was converted into 9,10-anhydro-*N*-(trifluoroacetyl)daunorubicin (**1**) in a single step, as previously described.[11] Mild hydrolysis of **1** in cold dilute base resulted in loss of the trifluoroacetyl group to give **2**. Reduction of **1** with hydrogen in the presence of palladium on alumina gave the 9-deoxydaunorubicin trifluoroacetamide, **4**, together with small amounts of two aglycons, 7-deoxy-9,10-anhydrodaunomycinone and 7,9-dideoxydaunomycinone. 9-Deoxydaunorubicin (**5**) was obtained from **4** by alkaline hydrolysis of the trifluoroacetamide. Gentle acid hydrolysis of **1** afforded the aglycon, 9,10-anhydrodaunomycinone (**3**), a compound which may have value in coupling reactions for the preparation of anthracycline analogues with fraudulent glycosides.

Although hydrolytic conversion of 9,10-anhydro-*N*-(trifluoroacetyl)adriamycin (**6**) to 9,10-anhydroadriamycin (**9**) is claimed without yield figures in the patent literature,[12] we found that the direct formation of **9** from **6**, in a manner analogous to the preparation of **2** from **1**, could not be accomplished because of the lability of the hydroxymethyl ketone side chain to alkaline conditions. Instead, in the present work, side-chain protection/deprotection (Scheme II), following the approach suggested by Vishnuvajjala et al.,[13] was used. Compound **6**, obtained from *N*-(trifluoroacetyl)adriamycin[2] in the usual manner, was converted into the *p*-anisyldiphenylmethyl ether **7**, which was then treated with base to give **8**. Gentle acid hydrolysis of **8** afforded the desired product, **9**. The 9,10-anhydroadriamycin aglycon (**10**) was prepared by acid hydrolysis of **6**. 9-Deoxyadriamycin, however, could not be prepared.

The corresponding 9-deoxy-*N*-(trifluoroacetyl)adriamycin 14-valerate (9-deoxy-AD 32, **11**) was made by hydrogenation of 9,10-anhydro-*N*-(trifluoroacetyl)adriamycin 14-valerate[11] in the presence of palladium on alumina.

All products appeared to be homogeneous (TLC and HPLC); structural assignments are consistent with spectral (IR, UV–Vis, and NMR) properties and microchemical analytical values. Because of poor NMR signal resolution at 60 MHz, selected compounds were further examined at higher field strength (Varian XL-100 spectrometer), courtesy of Dr. Walter Korytnyk, Roswell Park Memorial Institute. Thus, for the 9,10-anhydro compound **11**, 100-

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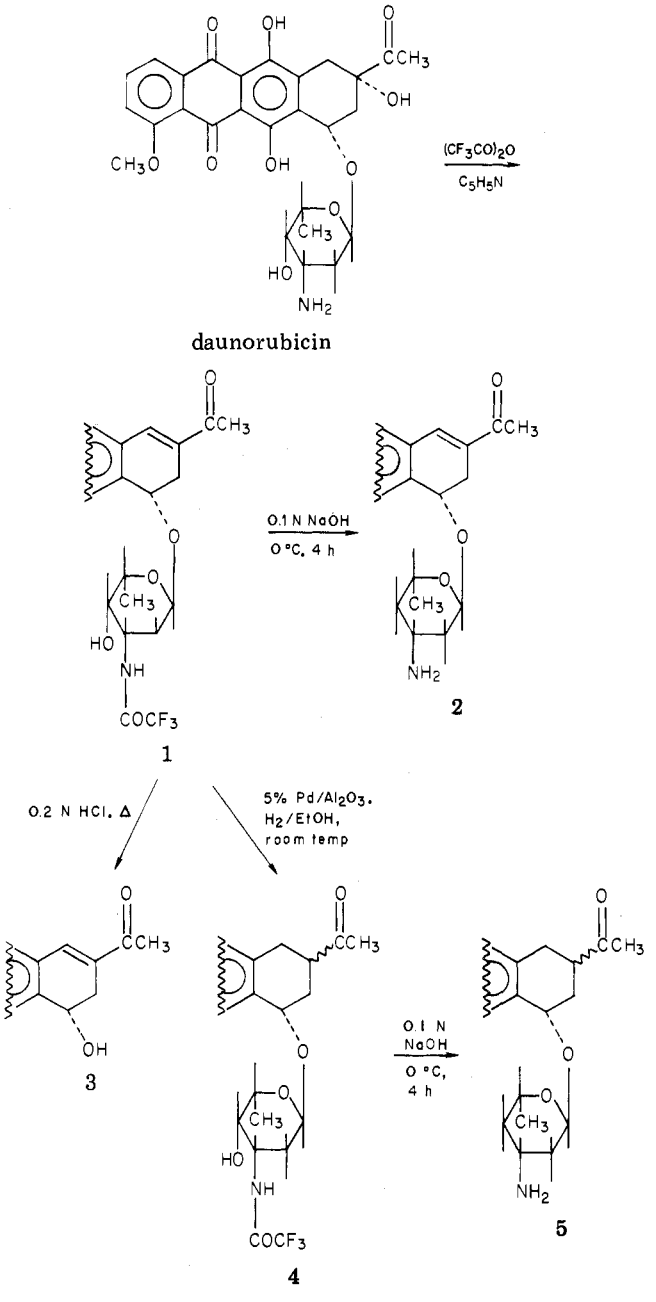
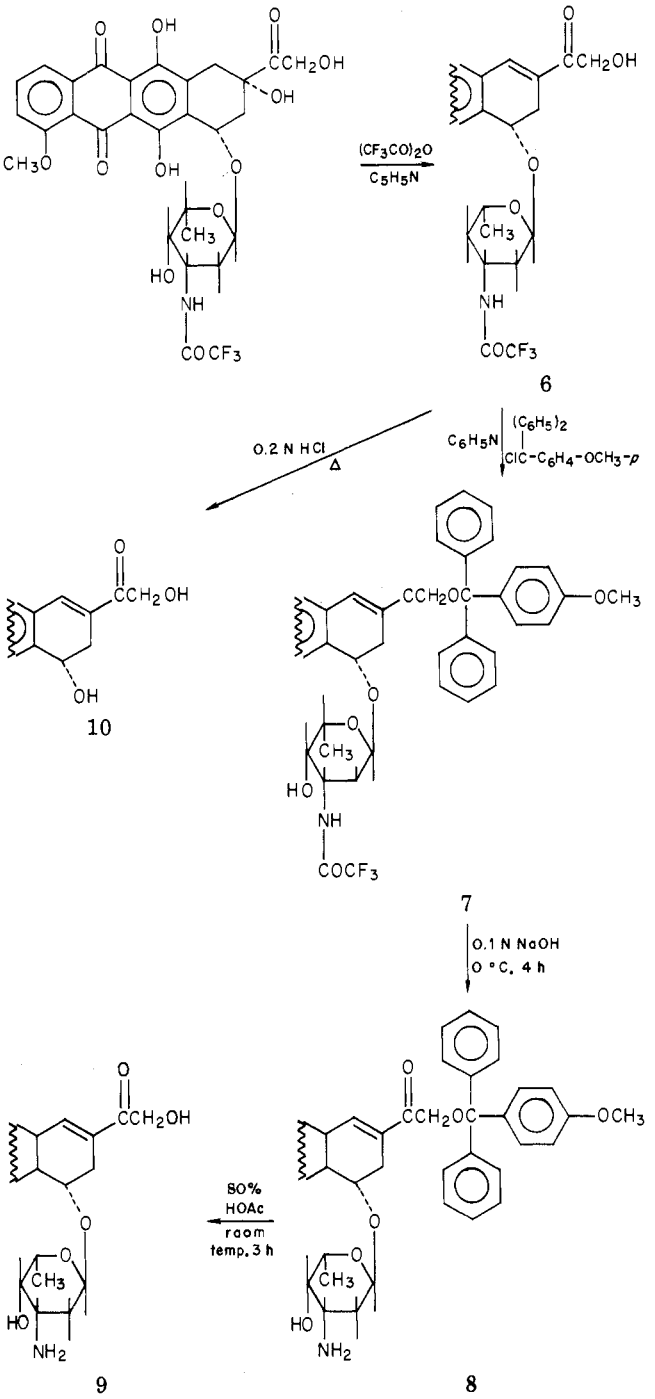
Scheme I



Scheme II



MHz NMR spectometry clearly revealed the C-10 vinylic proton (δ 7.97). Furthermore, the proton signal observable for the 9-OH of *N*-(trifluoroacetyl)adriamycin 14-valerate (δ 4.47, exchangeable) is not present in the spectrum of **11**, and the 10-CH_2 AB pattern of *N*-(trifluoroacetyl)adriamycin 14-valerate (δ 2.9–3.4) is absent in **11**. An additional notable spectral difference between these two compounds relates to the position of signals due to the phenolic protons. Because of the extension of conjugation in the 9,10-anhydro derivative, the separation of the phenolic protons in **11** is only 0.18 ppm (δ 13.47 and 13.65), compared to *N*-(trifluoroacetyl)adriamycin 14-valerate where the separation is 0.75 ppm (δ 13.06 and 13.81).

Despite the appearance of homogeneity on chromatography, the high-resolution spectrum of **4** showed it to be a diastereomeric mixture. Double signals of almost equal intensity were seen for the 6′-CH_3 (finely split doublet, δ 1.28, J = 6 Hz), the 9-$COCH_3$ (δ 2.30 and 2.34), the 1′-H (δ 4.5 and 5.5), and the phenolic regions (δ 13.19, 13.21, 13.80, and 13.90). Compared to the spectrum of *N*-(trifluoroacetyl)daunorubicin, that of **4** showed considerable change in the 10-CH_2 A + B pattern. However, because of the stereoisomeric nature of the sample, it was not possible to measure $J_{10A+B,9}$ or $J_{9,8A+B}$. Based upon the findings with **4**, the diastereomeric nature of **12** must also be inferred.

Target compounds were evaluated for in vitro growth-inhibitory activity against CCRF-CEM (human lymphoblastic leukemic) cells, according to previously described assay conditions;[14] the data are given in Table I. In all instances, the biological activity of the 9,10-anhydro derivative was less than that of its parent drug. It is unclear whether this reduction in activity is attributable to the loss of the tertiary carbinol or to the attendant configurational changes in the anthracycline A ring brought about by dehydration. Where the structurally related

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Table I. Molecular Formulas, Analytical Data, and in Vitro Cell Growth Inhibition Data

compd	formula	anal.[a]	ID_{50},[b] μM
daunorubicin			0.040[c]
adriamycin			0.066[c]
AD 32[c]			0.23[c]
1[d]			2.56[d]
2	$C_{27}H_{27}NO_9 \cdot HCl \cdot 2H_2O$	C, H, Cl, N	0.28
3	$C_{21}H_{16}O_7$	C, H	10.0
4	$C_{29}H_{28}F_3NO_{10}$	C, H, F, N	3.95
5	$C_{27}H_{29}NO_9 \cdot HCl$	C, H, N	0.33
6	$C_{29}H_{26}F_3NO_{11} \cdot H_2O$	C, H, F, N	5.79
7	$C_{49}H_{43}F_3NO_{12}$	C, H, F, N	>5.0
8	$C_{47}H_{44}NO_{11} \cdot HCl$	C, H, Cl, N	>5.0
9	$C_{27}H_{27}NO_{10} \cdot HCl$	C, H, Cl, N	2.31
10	$C_{21}H_{16}O_8$	C, H	
11[d]			2.70[d]
12	$C_{34}H_{36}F_3NO_{12}$	C, H, F, N	4.71
7-deoxy-9,10-anhydro-daunomycinone	$C_{21}H_{16}O_6$	C, H	>10.0
7,9-dideoxy-daunomycinone	$C_{21}H_{18}O_6$	C, H	>10.0

[a] Found values are within ±0.4% theory. [b] Concentration of drug inhibiting the growth of CCRF-CEM cultures by 50%, relative to untreated controls; 48-h incubations. [c] Reference 1. [d] Reference 11.

9-deoxy compounds were available for comparison, these agents, in general, were active to essentially the same extent as the corresponding 9,10-anhydro products. From a structure–activity point of view, these findings suggest that the 9-carbinol function of the daunorubicin/adriamycin-type of anthracycline contributes in some way to the expression of biological activity for these compounds. A similar conclusion has been arrived at by Henry[15] based upon a different line of structure–activity analysis. The present work should not be interpreted too narrowly, however, in view of the diastereomeric nature of the side chain in the 9-deoxy compounds described here.

Experimental Section

UV-Vis spectra were determined on a Cary Model 15 spectrophotometer in methanol. IR spectra were recorded as KCl pellets on a Perkin-Elmer Model 137B Infracord. Rotational data were obtained using a Perkin-Elmer Model 144Mc spectropolarimeter. Column chromatography was done in BioSil A silicic acid (100–200 mesh, Bio-Rad Laboratories). Microchemical analytical data, as determined by Galbraith Laboratories, Inc., Knoxville, TN, are included in Table I. Chromatographic evaluation of purity was accomplished by TLC [silica gel G glass-backed plates (Analtech), with either $CHCl_3$–MeOH–H_2O, 120:20:1, or $CHCl_3$–MeOH–H_2O, 80:30:3, as eluant] and/or HPLC [μ-Bondapak/phenyl (Waters Associates), CH_3CN–aqueous pH 4.0 ammonium formate buffer, flow fluorescence detection, excitation at 482 nm].

9,10-Anhydrodaunorubicin (2) Hydrochloride Dihydrate. To an ice-cold solution of 1[11] (120 mg, 0.20 mmol) in THF (20 mL) was added cold 0.1 N NaOH (20 mL) over a 10-min period. The reaction mixture was stirred at 0 °C for 4 h and then acidified to pH 6.0 by the addition of 0.1 N HCl (16 mL). THF was removed under reduced pressure, and the remaining solution was mixed with pH 10 buffer (20 mL). The aqueous solution was extracted with $CHCl_3$ (4 × 60 mL). The combined $CHCl_3$ extract was washed with distilled H_2O (3 × 100 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was redissolved in $CHCl_3$ (2 mL), ether (5 mL) was added, and the product was triturated with petroleum ether to give, after drying, 83 mg (82%) of red solid. The free base was converted into the hydrochloride salt by the addition of 0.1 N HCl (0.4 mL). 2-Propanol was added, and the mixture was evaporated to dryness; the residue crystallized from methanol–ethyl acetate to give 16 mg of **2** as the hydrochloride dihydrate: mp 188–191 °C dec (lit.[12] mp 185–186 °C dec); $[\alpha]_D$ +472° (*c* 0.012, methanol); IR 3425 (broad, OH, NH), 1705, 1688, 1620 (carbonyls) cm^{-1}.

9,10-Anhydrodaunomycinone (3). Compound 1 (50 mg, 0.083 mmol) was heated at reflux with 0.2 N HCl (20 mL) for 1 h. After the mixture was cooled, the precipitate was collected and washed with cold H_2O. The crude product was chromatographed on silicic acid with $CHCl_3$ as eluting solvent. The first set of fractions, containing **3**, were combined and evaporated to dryness to give 22 mg (70%) of product, mp 270–275 °C dec; IR 3470 (OH), 1710 and 1620 (carbonyl) cm^{-1}; UV-Vis λ_{max} 222 nm (ε 13 800), 234 (15 900), 269 (2200), 502 (13 000), 513 (12 800), 552 (7110).

9-Deoxy-*N*-(trifluoroacetyl)daunorubicin (4). A mixture of 1 (400 mg, 0.66 mmol) in methanol (30 mL, dried over molecular sieves) and 5% Pd/Al_2O_3 (80 mg) was shaken under H_2 in a Parr hydrogenator at an initial pressure of 50 psig. After 1.5 h, the reaction mixture was filtered with the aid of Celite, and the filtrate was evaporated in vacuo. The crude product was purified by chromatography on silicic acid, with $CHCl_3$ as eluant. The earliest fractions contained **7-deoxy-9,10-anhydrodaunomycinone** (20 mg), mp 155–160 °C. The next set of fractions contained **7,9-dideoxydaunomycinone** (22 mg), mp 240–245 °C (lit.[16] mp 244–245 °C). Finally, **4** was obtained: yield 93 mg (23%); mp 155–160 °C dec.

9-Deoxydaunorubicin (5) Hydrochloride. Compound 4 (90 mg, 0.15 mmol) was converted into **5** free base and then to the hydrochloride salt according to the procedure described above for the conversion of 1 into **2**: yield 58 mg (98%); mp 165–170 °C dec.

9,10-Anhydro-*N*-(trifluoroacetyl)adriamycin 14-*O*-(*p*-Anisyldiphenylmethyl) Ether (7). To 6[11] (300 mg, 0.48 mmol) in dry pyridine (75 mL, freshly distilled over KOH) was added *p*-anisyldiphenylchloromethane (2.8 g), and the reaction mixture was stirred at 65 °C for 6 h. The pyridine was evaporated under reduced pressure, and the residue was taken into $CHCl_3$ (300 mL). The $CHCl_3$ solution was washed with H_2O (4 × 100 mL) and dried over Na_2SO_4. Evaporation of the solvent, followed by chromatography on silicic acid, afforded 380 mg (89%) of product, mp 142–143 °C dec.

9,10-Anhydroadriamycin 14-*O*-(*p*-Anisyldiphenylmethyl) Ether (8) Hydrochloride. As for the preparation of **2** from 1, 68 mg (0.076 mmol) of **7** afforded 49 mg (77%) of **8** free base. A small quantity was converted into the hydrochloride (mp 175–180 °C dec) for analysis.

9,10-Anhydroadriamycin (9) Hydrochloride. Compound **8** (100 mg, 0.119 mmol) was taken into 80% aqueous acetic acid, and the mixture was stirred at room temperature for 3 h. Following the addition of H_2O and solid $NaHCO_3$ to adjust the pH to 8.0, the crude product was extracted into $CHCl_3$ containing 1% (v/v) of methanol (3 × 50 mL). The $CHCl_3$ extract was washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). Column chromatography separated **9** free base (27 mg, 40%) from small quantities of the aglycon. A portion of the free base was converted in the usual manner to the hydrochloride salt (mp 180–183 °C dec) for analysis.

9,10-Anhydroadriamycinone (10). Reaction of **6** (50 mg, 0.08 mmol) in 0.2 N HCl, with workup as for **3**, returned, after purification by column chromatography, 15 mg (47%) of analytically pure product, mp 264–269 °C dec.

9-Deoxy-*N*-(trifluoroacetyl)adriamycin 14-Valerate (12). 9,10-Anhydro-*N*-(trifluoroacetyl)adriamycin 14-valerate (11;[11] 100 mg, 0.142 mmol) in methanol (15 mL) was shaken under H_2 (initial pressure 50 psig) at room temperature for 2 h in the presence of 5% Pd/Al_2O_3 (30 mg). The catalyst was separated, and the filtrate was evaporated to dryness. Chromatography on silicic acid with $CHCl_3$ afforded 10 mg (10%) of product, mp 125–130 °C dec.

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Acknowledgment. The authors are especially grateful to Dr. Walter Korytnyk and Ms. Onda Simmons of Roswell Park Memorial Institute, Buffalo, NY, for obtaining and interpreting the 100-MHz NMR spectral data discussed in this report. We are further indebted to Adria Laboratories, Inc., Columbus, OH, and Farmitalia, Milan, Italy, for quantities of bulk daunorubicin and adriamycin hydrochlorides and to Dr. Jean M. Idriss of these laboratories for the cell culture determinations. These studies were supported by Research Grants CA 17263 and CA 19118 from the National Cancer Institute, National Institutes of Health, Bethesda, MD.

Synthesis and in Vitro Antimicrobial Activity of 6-Substituted 2*H*-1,3,5-Thiadiazine-2,4(3*H*)-diones

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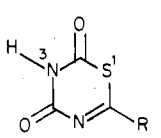
A series of 6-substituted 2*H*-1,3,5-thiadiazine-2,4(3*H*)-diones (**1a–m**) was prepared by treatment of alkyl, aryl, and heterocyclic primary thioamides with phenoxycarbonyl isocyanate to give *N*-(phenoxycarbonyl)-*N'*-thioacylureas, which gave 1 upon heating in refluxing xylene solution or upon treatment with aqueous sodium carbonate solution followed by acidification. ^{1}H NMR and infrared spectral evidence indicates that the 6-alkyl derivatives **1a,b,l,m** exist predominately in the exocyclic alkylidene tautomeric form. The major product obtained from alkaline and acid hydrolysis of the 6-phenyl derivative **1c** was found to be benzoic acid and benzoylurea, respectively. The majority of compounds **1a–m** exhibited in vitro antifungal activity against *Candida albicans* and *Trichophyton mentagrophytes*. Several derivatives, **1b–d,h,j**, displayed minimum inhibitory concentration values below 2 μg/mL against *Trichophyton mentagrophytes*. Four derivatives, **1c,e,g,h**, inhibited the growth of *Seratia marcesens*, *Staphylococcus aureus*, and *Staphylococcus epidermis* in an in vitro sensitivity disk assay. 2-Furyl derivative **1h** displayed antileukemic activity against P-388 lymphocytic leukemia.

Heteroatom-modified analogues of uracil and its 5- or 6-substituted derivatives have represented a productive source of compounds exhibiting antimicrobial, cytostatic, or virostatic activities, presumably involving antimetabolic mechanisms of action.[2] 3-Oxauracils,[3] 5,6-dihydro-6-oxauracil,[4] 5- and 6-azauracil,[5,6] 6-azathymine,[7] and 5-azaorotate[8] are examples of such analogues displaying one or more of the above activities. Our interest in isoconjugate analogues of biologically important pyrimidine and purine derivatives[9-11] has prompted the investigation of 2*H*-1,3,5-thiadiazine-2,4(3*H*)-diones, **1**, which may be regarded as 6-substituted 5-thiauracils. The synthesis of **1**, examination of its aqueous stability, and a preliminary evaluation of in vitro antimicrobial properties are described for 14 derivatives in this class.



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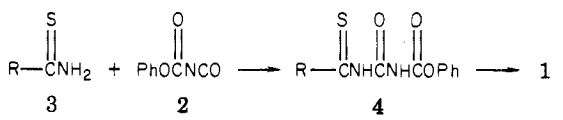
Chemistry. Previously reported[12,13] syntheses of 3-aryl or 3-thiocarbonyl derivatives of **1** are unsuitable for the preparation of the desired 3-unsubstituted derivatives, since the heterocyclic ring is unlikely to survive conditions necessary for the removal of the 3-substituent. Uracils have been synthesized by the reaction of enamines with phenoxycarbonyl isocyanate[14] (**2**), which has also been shown to be useful in the preparation of mesoionic xanthine and uracil analogues.[15,16] The reaction of primary thioamides **3** with **2** in toluene gives *N*-(phenoxycarbonyl)-*N'*-thioacylureas, **4** (Scheme I).

Scheme I



3 **2** **4**

Table I. *N*-(Phenoxycarbonyl)-*N'*-thioacylureas

no.	R	mp,[a] °C	formula[b]	yield, %
4a	*i*-C_3H_7	155-157	$C_{12}H_{14}N_2O_3S$	71
4b	$CH_2C_6H_5$	129-130	$C_{16}H_{14}N_2O_3S$	70
4c	C_6H_5	159-161	$C_{15}H_{12}N_2O_3S$	85
4d	4-$CH_3C_6H_4$	158-160	$C_{16}H_{14}N_2O_3S$	76
4e	4-ClC_6H_4	133-135	$C_{15}H_{11}ClN_2O_3S$	78
4f	4-$(CH_3)_2NC_6H_4$	162-164	$C_{17}H_{17}N_3O_3S$	67
4g	2-thienyl	165-167	$C_{13}H_{10}N_2O_3S_2$	70

[a] All compounds were recrystallized from $CHCl_3$-petroleum ether (bp 40-60 °C) and melted with decomposition. [b] All compounds analyzed for C, H, and N within ±0.4% of theoretical values.

In a number of cases, **4a–g**, these intermediates were isolated and characterized (Table I). In one case, where R = *tert*-butyl, the products of this reaction were phenyl

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