treated with a saturated Me_2CO solution of fumaric acid. The precipitate was filtered after 2 hr to furnish 2.8 g of the desired product, mp 209–212° dec. The presence of the other isomer VIIa was not detected. Anal. ($C_{21}H_{20}F_6N_2O_5$) C, H, N.

Method B. A solution of 4.8 g of the ketone XI in 120 ml of EtOH and 3 ml of HCl was hydrogenated in the presence of PtO_2 at 4.2 kg/cm² for 8 hr. After removal of the catalyst, the solution was evaporated to dryness. The residue was made basic with aqueous NaOH and the base was taken into 300 ml of Et_2O. The Et_2O solution was washed (H_2O), dried ($MgSO_4$), and treated with fumaric acid solution in Me_2CO. There was obtained 1.7 g of the product (mp 209–212°) which was shown to be identical with the lower melting isomer VIIb obtained in the preceding experiment.

α-(3-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol Fumarate. Higher Melting Isomer VIIa. From the mother liquor of the preceding experiment, there was isolated 0.2 g of a solid product, mp 230–235°. On recrystallization from MeOH, a pure sample was obtained as white crystals, mp 264–266° dec, which was shown to be totally different from the other isomer VIIb. Anal. ($C_{21}H_{20}F_6N_2O_5$) C, H, N.

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Synthesis and Antiinflammatory Properties of N-Substituted 4,5-Dioxopyrrolidine-3-carboxanilides*

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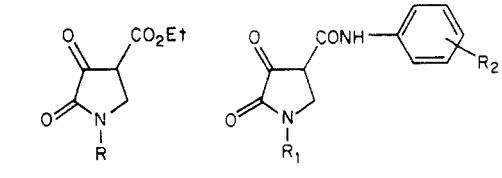
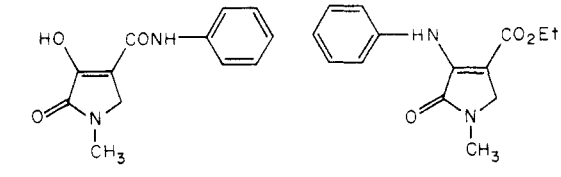
The synthesis and physical properties of a series of *N*-methyl- and *N*-phenyl-4,5-dioxopyrrolidine-3-carboxanilides are described. Unlike previously reported carboxanilides derived from 1,3(2*H*,4*H*)-dioxoisoquinoline and 2-oxobenzofuran, the currently described agents exist solely as the enol tautomers and, as a result, do not display comparable acidic properties. None of the newly reported compounds exhibited activity equal to that of aspirin in the carrageenin-induced rat foot edema assay.

The finding that certain carboxylic acid amides bearing suitably acidic protons at a position α to the amide carbonyl group also exhibit antiinflammatory properties was first reported in 1969[1] and has since been the subject of a detailed review.[2] The ready availability of 4,5-dioxopyrrolidine-3-carboxylic acid esters[3,4] (I) prompted the synthesis and pharmacologic examination of related amides having structural features in common with previously reported anilides displaying antiinflammatory activity.[1,2] Although Beckett et al.[5] reported that no important pharmacologic properties were manifested by N-substituted 4,5-dioxopyrrolidine-3-carboxylic acid esters, they failed to prepare any of the corresponding amide derivatives.

When ethyl N-substituted-4,5-dioxopyrrolidine-3-carboxylates (I) were allowed to react with aniline and substituted anilines in refluxing xylene, generally excellent yields of the respective anilides II were obtained (Table I). Like the esters (I) utilized as starting materials, reported by Beckett et al.[5] to exist in solution solely in the enolic form, but unlike previously reported anilides derived from 1,3(2*H*,4*H*)-dioxoisoquinoline[6] and 2-oxobenzofuran,[7] compounds of type II also exist in the enolic configuration. For example, the NMR spectrum of II (R_1 = CH_3, R_2 = H) exhibits, in addition to the aromatic and *N*-methyl signals, singlets at δ 9.2 (1 H), disappearing upon the addition of D_2O, and at δ 4.02 (2 H). The fact that neither of these signals, the former due to the enolic proton and the latter to the methylene hydrogens of the pyrrolidine ring, is split is consistent with the assignment of the enolic configuration III.

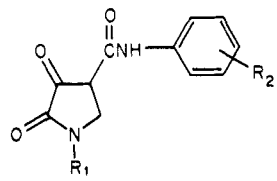




In comparison to those carboxanilides derived from 1,3(2*H*,4*H*)-dioxoisoquinoline[6] and 2-oxobenzofuran,[7] the anilides described in Table I displayed only moderately acidic properties despite the activation afforded the ionizing group by the presence of an adjacent carbonyl function and a vinylogous amide moiety. The reason for

* This note is dedicated to the memory of Professor Edward E. Smissman.

Table I. Physical Properties of N-Substituted 4,5-Dioxopyrrolidine-3-carboxanilides



Compd	R_1	R_2	Mp, °C	Solvent of recrystn	Formula[a]	pK_a'[b]
1	CH_3	H	229 dec	HOAc	$C_{12}H_{12}N_2O_3$	5.86
2	CH_3	4-OCH_3	221 dec	DMF-CH_3CN	$C_{13}H_{14}N_2O_4$	5.84
3	CH_3	4-Cl	238 dec	HOAc	$C_{12}H_{11}ClN_2O_3$	5.51
4	CH_3	4-CF_3	236 dec	HOAc	$C_{13}H_{11}F_3N_2O_3$	
5	CH_3	4-F	229 dec	DMF-CH_3CN	$C_{12}H_{11}FN_2O_3$	5.55
6	CH_3	4-CH_3	226 dec	DMF-CH_3CN	$C_{13}H_{14}N_2O_3$	5.79
7	CH_3	2-CO_2Et	199 dec	Xylene	$C_{15}H_{16}N_2O_5$	6.49
8	CH_3	2-OCH_3	216 dec	Xylene	$C_{13}H_{14}N_2O_4$	6.08
9	C_6H_5	H	246 dec	HOAc	$C_{17}H_{14}N_2O_3$	5.58
10	C_6H_5	4-OCH_3	240 dec	HOAc	$C_{18}H_{16}N_2O_4$	
11	C_6H_5	4-Cl	253 dec	HOAc	$C_{17}H_{13}ClN_2O_3$	
12	C_6H_5	4-CF_3	264 dec	DMF-CH_3CN	$C_{18}H_{13}F_3N_2O_3$	
13	C_6H_5	2-OCH_3	250 dec	DMF-CH_3CN	$C_{18}H_{16}N_2O_4$	6.19
14	C_6H_5	2-Cl	261 dec	DMF-CH_3CN	$C_{17}H_{13}ClN_2O_3$	
15	C_6H_5	2-CF_3	247 dec	HOAc	$C_{18}H_{13}F_3N_2O_3$	5.87

[a] All analyses are within ±0.35% of calculated values. [b] See Experimental Section.

this disparity in pK_a' values may be due, in part, to the fact that compounds of type II can achieve a favorable energy state as a consequence of enolization which is accompanied by resonance and hydrogen bonding stabilizing influences, whereas steric encumbrances to enolization lead to facilitation of the ionization that occurs in 1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxanilides and 2-oxobenzofuran-3-carboxanilides. When the pK_a' values of the *N*-methyl-4,5-dioxopyrrolidine-3-carboxanilides were plotted against the pK_a values of the correspondingly substituted anilines, a linear free-energy relationship was not obtained, indicating that substituent polar effects in this system were not uniformly transmitted to the acidic functionality,[8-10] probably because the hydrogen bond formed by the enolic proton demonstrates no particular preference either for the lactam or carboxanilide carbonyl oxygen.

Treatment of I (R = CH_3) with aniline in refluxing ethanol led only to the enamine IV. That the latter material exists as depicted and not as the imine was shown by its NMR spectrum which exhibited, in analogy with the spectra of I and II, singlets at δ 8.54 (hydrogen on aniline nitrogen) and δ 3.3 (methylene protons of pyrrolidine ring). Why the use of xylene as a solvent leads to the formation of II while the use of ethanol results in the synthesis of IV is not clear.

While all of the substances reported in Table I displayed a minor degree of antiinflammatory activity when tested orally in the carrageenin-induced rat foot edema assay procedure[11] at doses of 33 mg/kg, none exhibited activity equal to that shown by an oral dose of 100 mg/kg of aspirin (~50% inhibition) in the same screen.

Experimental Section

Melting points are uncorrected. NMR spectra of Me_2SO-d_6 solutions were recorded on a Varian A-60 spectrometer (Me_4Si). pK_a' determinations were performed at 25° in 1:2 (v/v) H_2O–dioxane using a Metrohm automatic potentiograph (Model E436). Compounds for which no pK_a' data are reported were insufficiently soluble. Both ethyl *N*-methyl-4,5-dioxopyrrolidine-3-carboxylate[4] and ethyl *N*-phenyl-4,5-dioxopyrrolidine-3-carboxylate[3] were prepared as previously described.

Anilides II were prepared by allowing equimolar quantities of I and the appropriately substituted aniline to react in refluxing xylene for 2–5 hr during which time solvent was slowly removed by means of a still head. Xylene was added occasionally in order to maintain volume. The products precipitated during reflux and, after cooling, were filtered, dried, and recrystallized. Yields ranged from 60 to 95%.

Ethyl *N*-Methyl-5-oxo-4-phenyliminopyrrolidine-3-carboxylate (IV). A solution of 1.9 g (0.01 mol) of ethyl *N*-methyl-4,5-dioxopyrrolidine-3-carboxylate and 0.93 g (0.01 mol) of aniline in 10 ml of ethanol was refluxed for 21 hr. Upon cooling a precipitate formed. Filtration and recrystallization from ethanol afforded 2.0 g (77%) of material, mp 143–144°. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.43; H, 6.18; N, 10.97.

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