Arylsuccinimides. I. Alkylation and Acylation Studies

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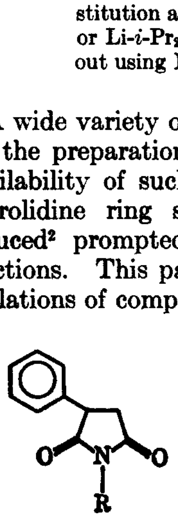
Alkylation of a series of phenylsuccinimides has been studied with several base–solvent combinations. Substitution at the 4 position in preference to the 3 position was observed in several cases when excess $NaNH_2$–NH_3 or Li-*i*-Pr_2N–Et_2O was employed. Acylations and dialkylations of 3,3-disubstituted succinimides were carried out using NaH–THF.

A wide variety of synthetic methods have been used for the preparation of arylsuccinimides.[1b] The ready availability of such systems and the ubiquity of the pyrrolidine ring system to which they are easily reduced[2] prompted us to investigate some of their reactions. This paper describes some alkylations and acylations of compounds of types **1**, **2**, and **3**.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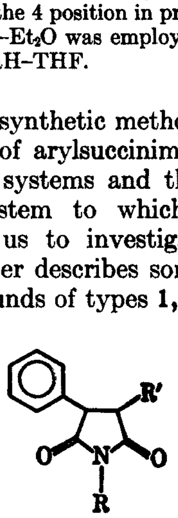
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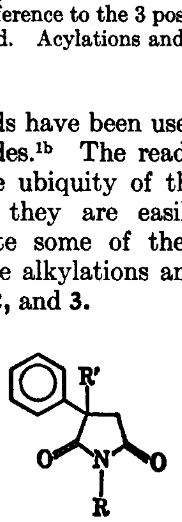
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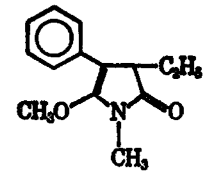
It would certainly be expected that alkylation in any of these systems in which R = H would occur first on nitrogen, although Hauser[3] has shown that succinimide itself will undergo C rather than N alkylation with 2 equiv of potassium amide in liquid ammonia. Excellent yields of N-substitution products can be obtained from succinimides using sodium amide in xylene or even potassium hydroxide in alcohol. Indeed N-acyl derivatives are formed using an acyl halide in pyridine.[4]

For systems carrying a substituent on nitrogen, substitution would be expected to occur at the ring position bearing the phenyl group in **1** and **2** since this is activated by two groups. When **2** (R = CH_3; R′ = C_2H_5) was treated with methyl iodide and sodium hydride in DMF, an 85% yield of the 3-methyl derivative was obtained, contaminated with about 10% of what is probably enol ether **4**. In like fashion, N-benzoyl derivative **2** (R = COC_6H_5; R′ = C_2H_5) was converted in moderate yield into **5** after hydrolysis.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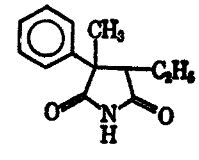
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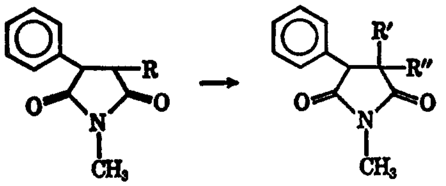
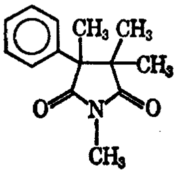
When alkylation was carried out on these systems with excess sodium amide in liquid ammonia or excess lithium diisopropylamide (LDIPA) in ether, however, quite different results were obtained. With these base–solvent combinations, alkylation occurred at the 4 position of the ring instead of the expected 3 position. In each case, a yellow precipitate formed on addition of **1** or **2** to the solution of the base, and the precipitate dissolved gradually on addition of alkyl halide. Subsequent work-up yielded the 4,4-disubstitution product. For 1-methyl-3-phenylsuccinimide (**1**, R = CH_3) at least 3 mol of base and 2 mol of halide were used to produce the disubstitution product, while lesser proportions gave mixtures of products and starting material, probably because the monoalkylation product in solution competed successfully for the halide with the starting material which was present at least partially as a precipitate. With type **2** compounds, at least 2 mol of base and 1 mol of halide gave good yields of mixtures of isomers of the 4-substitution product. Table I summarizes the 4 alkylations carried out in this way (eq 1).


(1)

Starting materials of type **2** already carrying one 4 substituent gave almost exclusively 4 alkylation and very little 3 alkylation except for the case of **2** (R′ = CH_3) where a small amount of 3 alkylation was detectable (by nmr, see below). 1-Methyl-3-phenylsuccinimide (**1**, R = CH_3), on the other hand, gave mixtures of products depending on base–solvent and halide used. With excess methyl iodide and $NaNH_2$–NH_3, the product was chiefly the completely alkylated **9**, while with excess ethyl iodide and LDIPA–ether the product was largely the 4,4-disubstitution product (**10**, R = C_2H_5). Methyl iodide with LDIPA–ether and ethyl iodide with $NaNH_2$–NH_3 gave mixtures of reaction types. Type **3** (R′ = CH_3) was not 4 substituted by ethyl iodide with $NaNH_2$–NH_3 under these conditions, although such an alkylation was realized with a different base–solvent (see below).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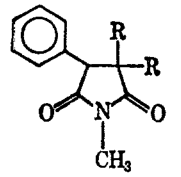
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[1] (a) To whom all correspondence should be addressed at E. R. Squibb & Sons, New Brunswick, N. J. (b) C. A. Miller and L. M. Long, *J. Amer. Chem. Soc.*, **75**, 6256 (1953); R. Robbin, *Bull. Soc. Chim. Fr.*, 2275 (1965); R. Carrie, *C. R. Acad. Sci., Paris*, **251**, 2981 (1960); A. Foucaud, *ibid.*, **246**, 3257 (1958); G. Poulain, *Bull. Soc. Chim. Fr.*, 913 (1964).

[2] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, New York, N. Y., 1956, pp 634 ff.

[3] D. R. Bryant and C. R. Hauser, *J. Amer. Chem. Soc.*, **83**, 3468 (1961).

[4] British Patent 844,267 (Aug 10, 1960).

TABLE I

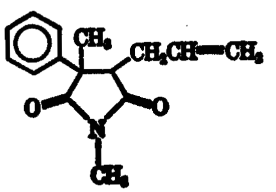
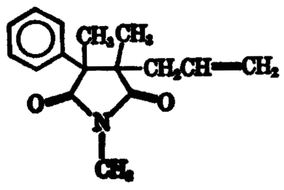
4 ALKYLATIONS OF 3-ARYLSUCCINIMIDES (EQ 1)

R	R′	R″	Base-solvent	Halide	Bp (mm) or mp, °C	Crude yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
H	CH_3	CH_3	LDIPA–Et_2O	CH_3I	118–119 (0.03)	*a*					
H	CH_3	CH_3	$NaNH_2$–NH_3	CH_3I	128–131 (0.1)	*b*					
H	C_2H_5	C_2H_5	LDIPA–Et_2O	C_2H_5I	126–134 (0.1)	*c*					
H	C_2H_5	C_2H_5	$NaNH_2$–NH_3	C_2H_5I	131–134 (0.1)	*d*					
H			Either	$Br(CH_2)_4Br$		0[e]					
H			Either	$Br(CH_2)_5Br$		0[e]					
CH_3	CH_3	CH_3	$NaNH_2$–NH_3	CH_3I	129–134 (0.3)[f] 68–69	58	$C_{13}H_{15}NO_2$	71.87	72.07	6.96	7.15
C_2H_5	CH_3	C_2H_5[g]	$NaNH_2$–NH_3	CH_3I	126–127 (0.3)	95	$C_{14}H_{17}NO_2$	72.70	72.54	7.41	7.29
C_2H_5	CH_3	C_2H_5	LDIPA–Et_2O	CH_3I	120–122 (0.05)	83					
C_2H_5	C_2H_5	C_2H_5	$NaNH_2$–NH_3	C_2H_5Br	134–136 (0.3)	95[h]	$C_{15}H_{19}NO_2$	73.44	73.65	7.81	8.00
C_2H_5	$CH_2{=}CHCH_2$	C_2H_5	LDIPA–Et_2O[i]	$CH_2{=}CH_2CH_2Br$	135–138 (0.3)	73	$C_{16}H_{19}NO_2$	74.68	74.80	7.44	7.74
$CH_2C_6H_5$	C_2H_5	$CH_2C_6H_5$	LDIPA–Et_2O	C_2H_5I	180–185 (0.3)[j]	81	$C_{20}H_{21}NO_2$	78.14	78.14	6.89	6.86

[a] A 0.25-mol run gave 29 g of product whose nmr spectrum indicated that 58% of the 3 proton remained. [b] A 0.25-mol run gave 57 g of product whose nmr spectrum showed it to be impure 9. [c] A 0.25-mol run gave 44 g of product whose nmr spectrum indicated that 73% of the 3 proton remained. [d] A 0.25-mol run gave 51 g of product whose nmr spectrum indicated that 62% of the 3 proton remained. In another run using only 1.1 equiv of C_2H_5I, nmr indicated a complex mixture of starting material and substitution products. [e] Starting imide recovered. Nmr on crude product showed that some 3 alkylation had occurred. [g] Nmr indicates slight difference in isomer content from previous run. [h] Same result obtained when either only 1.1 equiv of halide or 4 equiv used. [i] Less satisfactory results obtained with $NaNH_2$–NH_3. [j] Nmr indicated that some O alkylation had occurred.

TABLE II

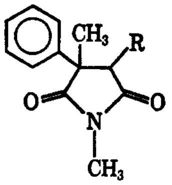
ALKYLATION OF 3-PHENYL-1,3-DIMETHYLSUCCINIMIDE WITH SODIUM HYDRIDE–TETRAHYDROFURAN (EQ 2)

Halide	Product(s)	Bp (mm) or mp, °C	Crude yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
CH_3I	c, R = CH_3	99–101[a]	26	$C_{14}H_{17}NO_2$	72.70	72.50	7.41	7.42
C_2H_5I	c, R = C_2H_5	90–92[b]	40[c]	$C_{16}H_{21}NO_2$	74.09	73.97	8.16	8.21
n-C_3H_7I	c, R = *n*-C_3H_7	66–67[d]	38	$C_{18}H_{25}NO_2$	75.22	75.30	8.77	8.98
i-C_3H_7Br	b, R = *i*-C_3H_7	115–117[a]	10[e]	$C_{15}H_{19}NO_2$	73.44	73.65	7.81	8.08
$CH_2{=}CHCH_2Br$	c, R = $CH_2CH{=}CH_2$	135–138 (0.3)	46	$C_{18}H_{21}NO_2$	76.29	76.29	7.47	7.57
$HOCH_2CH_2Br$	b, R = CH_2CH_2OH	155–160 (0.3)	32[f]	$C_{14}H_{17}NO_3$	68.00	68.15	6.93	7.23
$Br(CH_2)_4Br$	c, R + R = $-(CH_2)_4-$	108–110[a]	56	$C_{16}H_{19}NO_2$	74.68	74.70	7.44	7.51
$Br(CH_2)_5Br$	c, R + R = $-(CH_2)_5-$	80–81[g]	82	$C_{17}H_{21}NO_2$	75.24	75.02	7.80	7.99
trans-$BrCH_2CH{=}CHCH_2Br$	c, R + R = $-CHCH{=}CH_2$ $-CH_2$	140–142 (0.3)	26[e,f]	$C_{16}H_{17}NO_2$	75.27	75.40	6.71	7.01
CH_3I on 		125–135 (0.4)	79	$C_{16}H_{19}NO_2$	74.68	74.60	7.44	7.35
CH_3I on 1	c, R = CH_3	*h*	77					

[a] From benzene–petroleum ether. [b] From ethanol. [c] A run with equivalent quantities of halide and imide gave a mixture of a + b + c. [d] From methanol–water. [e] Purified by chromatography on neutral alumina. [f] 1.30:1.0 halide–imide used. [g] From ethanol–water. [h] Identical with material prepared above.

TABLE III

ACYLATIONS OF 3-PHENYL-1,3-DIMETHYLSUCCINIMIDE WITH SODIUM HYDRIDE–TETRAHYDROFURAN



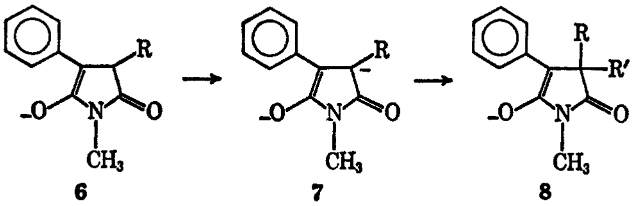
Acylating agent	Product, R	Bp (mm) or mp, C	Crude yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
Diethyl carbonate	$CO_2C_2H_5$	148–150 (0.2)	90	$C_{15}H_{17}NO_4$	65.44	65.14	6.22	6.12
Ethyl formate	$=CHOH$	188–189[a]	75	$C_{13}H_{13}NO_3$	67.52	67.23	5.67	5.83
Ethyl acetate	$=COHCH_3$	139–140 (0.3) 67–68	80	$C_{14}H_{15}NO_3$	68.55	68.37	6.16	6.08
Ethyl oxalate	$=COHCO_2C_2H_5$	98–99[c]	66	$C_{16}H_{17}NO_5$	63.35	63.08	5.65	5.66
Ethyl benzoate	$-COC_6H_5$	109–113[c] Softens 86	62	$C_{19}H_{17}NO_3$	74.25	73.95	5.57	5.69

[a] From EtOH–H_2O. [b] From MeOH–H_2O. [c] From benzene–petroleum ether.

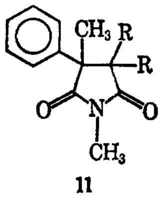
Gassman[5] has recently reported the successful alkylation of the related N-methylpyrrolidone using $NaNH_2$–NH_3.

We postulate that these 4 alkylations proceed through a dianion (**7**) as shown in Scheme I, reminiscent of the dianions studied by Hauser.[6] This alkylates at the more nucleophilic 4 position to give monoanion **8.** This can then form a second dianion when R = H and undergo a second alkylation at the 4 position to give **8** (R = R′). That **8** does not alkylate further is explicable on steric grounds. The geminal alkyl groups interacting with the phenyl group would be expected to stabilize the enol form of monosalt **8,** since this staggers the phenyl group with respect to the alkyl groups, and this effectively blocks the 3 position. Alkylation on oxygen is hindered by the N-methyl group as well as the phenyl group.

SCHEME I



Alkylation of type **3** imides was successful using sodium hydride in tetrahydrofuran. This base–solvent combination readily introduced two groups into the 4 position of 1,3-dimethyl-3-phenylsuccinimide (**3,** R = R′ = CH_3) to give products of type **11** with excess halide. Lesser proportions of halides gave difficult mixtures of products and starting material. Table II lists the alkylations of this type (eq 2) that were carried out.



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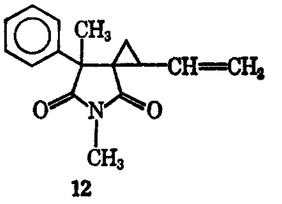

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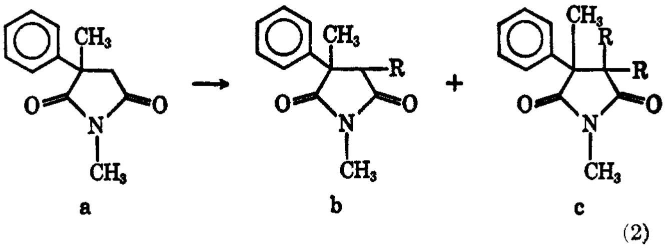
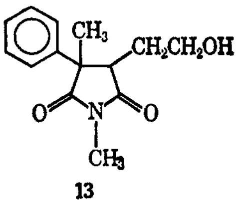
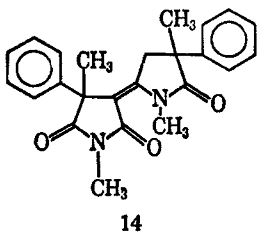


(2)

Needles and Whitfield[7] have reported recently that the related N,N-dimethylacetamides gave mixtures of starting material, mono- and dialkylation products with $NaNH_2$ in refluxing benzene or toluene. We have found that NaH–THF worked well with a variety of bromides and iodides including dihalides and some functional halides but not with chlorides. 1,4-Dibromobutane and 1,5-dibromopentane formed the corresponding spiro derivatives even when excess halide was employed. 1,3-Dibromopropane gave intractable mixtures of products and 1,2-dibromoethane failed to alkylate at all. *trans*-1,4-Dibromo-2-butene yielded cyclopropane derivative **12.** Kierstead,[8] Nickl,[9] and Korte[10] have shown that such *trans*-1-4-dihalobutenes yield vinylcyclopropanes on reaction with active methylene compounds. Only monoalkylation in low yield occurred with isopropylbromide, and bromoethanol gave **13** and some of the self-condensation product **14.**



13



14

When 3-bromopropanol was used, only **14** was obtained, no normal alkylation being observed. The preparation

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(5) P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **31,** 982 (1966).

(6) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **30,** 61 (1965), and earlier references cited therein.

(7) H. L. Needles and R. E. Whitfield, *ibid.*, **31,** 989 (1966).

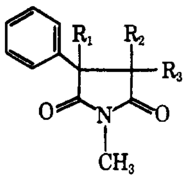
(8) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610, 3616 (1952); 1799, 1803 (1953).

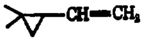
(9) J. Nickl, *Ber.*, **91,** 553 (1958).

(10) F. Korte, D. Scharf, and K.-H. Büchel, *Ann.*, **664,** 97 (1963).

TABLE IV

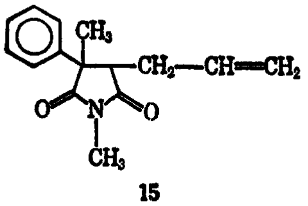
PERTINENT NMR DATA[a] (IN CARBON TETRACHLORIDE, δ)



R1	Registry no.		R2		R3	
H	86-34-0	3.87 ABX q[b]	H	ABX[c]	H	
H	19362-47-1	4.0 d, $J = 7$[d] 3.43 d, $J = 7$	H	2.66[c]	CH_3	1.29 d, $J = 7$ 0.73 d, $J = 7$
H	19362-48-2	3.70	CH_3	1.35	CH_3	0.76
CH_3	77-41-8	1.60	H	AB 3.00 d, $J = 18$ 2.73 d, $J = 18$	H	
CH_3	19362-50-6	1.55	CH_3	1.28	CH_3	0.70
H	19362-51-7	3.53 d, $J = 6$	H	2.73[e]	C_2H_5	0.95 t, $J = 7$
H[f,g]	19362-52-8	3.88 d, $J = 6$	H	3.10[e]	C_2H_5	1.08 t, $J = 6$
H	19362-53-9	3.78 s[d] 3.83 s	CH_3	1.37 0.73	C_2H_5	c
H	19362-54-0	3.89	C_2H_5	0.63 t, $J = 6$	C_2H_5	0.95 t, $J = 6$
H	19362-55-1	4.13 s[d] 3.97 s	C_2H_5	c	$CH_2CH{=}CH_2$	4.5–6.1 c
H	19362-56-2	3.53 d[h]	H	Obscured	$CH_2C_6H_5$	3.02 d?[h]
H[g]	19362-57-3	4.00	C_2H_5	1.45 q, $J = 7$ 0.74 t, $J = 7$	$CH_2C_6H_5$	3.49 d, $J = 23$, 1 H 2.69 d, $J = 23$, 1 H
CH_3[d,g]	19362-58-4	1.76 s 1.67 s	C_2H_5	c	H	Obscured
CH_3[d,i,j]	60-45-7	1.67 s 1.52 s	C_2H_5	0.97 t, $J = 6$ 0.80 t, $J = 6$	H	2.87 t, $J = 6$ 2.64 t, $J = 6$
CH_3	19362-60-8	1.64	C_2H_5	c	C_2H_5	c
CH_3	19362-61-9	1.63	C_3H_7	0.3–1.9 c	C_3H_7	0.3–1.9 c
CH_3	19362-62-0	1.64	$CH_2CH{=}CH_2$	2.58	$CH_2CH{=}CH_2$	2.46
CH_3	19362-63-1	1.57	$-(CH_2)_4-$[k]			
CH_3	19362-64-2	1.53	$-(CH_2)_5-$[k]			
CH_3[d]	19362-65-3	1.57 s 1.47 s				5.73–6.35 c, 1 H 4.65–5.40 c, 2 H 0.75 q[l]
CH_3	19362-66-4	1.65	i-C_3H^7	1.60 broad, 1 H 0.91 d, $J = 7$, 3 H 0.62 d, $J = 7$, 3 H	H	2.50 d, $J = 5$
CH_3[d]	19362-67-5	1.66 s 1.47 s	C_2H_4OH broad		H	Obscured
CH_3[d]	19362-68-6	1.67 s 1.52 s	$CH_2CH{=}CH_2$	6.1–4.4	H	2.6[m]
CH_3[d]	19362-69-7	1.67 s 1.55 s	$CH_2CH{=}CH_2$	5.8–4.4	CH_3	1.28 s, 0.74 s } 3 H
CH_3[d]	19362-70-0	1.73 s 1.53 s	$CO_2C_2H_5$	1.28 t, 0.75 t, $J = 7$, 3 H 4.23 q, 3.54 q, $J = 7$, 2 H	H	3.90 s, 3.60 s } 1 H
CH_3[n]	19362-71-1	2.09 s	$=CHOH$			
CH_3[g]	19362-72-2	1.78 s	$=COHCH_3$	1.69 s, 3 H 11.85, 1 H		
CH_3[g]	19362-73-3	1.95	$=COHCO_2C_2H_5$	4.05 s, $J = 7$, 2 H 1.04 t, $J = 7$, 3 H 12.2 broad, 1 H		
CH_3	19362-74-4	1.47 s	$COC_6H_5 \rightleftharpoons COHC_6H_5$	4.84 s ~ 0.5 H ~12.0 broad, ~0.5 H		

[a] s = singlet, d = doublet, t = triplet, q = quartet, c = complex, H = proton. Aromatic in range 7.20–7.36; NCH_3 in range 2.89–3.08. [b] 3.77, 3.83, 3.91, 3.97. [c] Partially obscured by NCH_3. [d] Mixture of diastereomers indicated. [e] Six-line pattern for M of AMX_2 partially obscured by NCH_3. [f] N-Benzoyl compound. [g] Run in $CDCl_3$. [h] Poorly resolved. [i] NH compound. [j] Aromatic shows as two singlets. [k] Broad envelope. [l] Only clearly resolved X part of ABX pattern; 0.85, 0.75, 0.70, 0.60; rest is obscured. [m] Obscured by $CH_2C{=}$. [n] Run in pyridine.

of **16** by the alkylation of **15** illustrates the utility of this procedure for the preparation of imides with different 4 substituents. Alkylation of **1** (R = CH_3) under these conditions produced a good yield of the completely methylated derivative **9**.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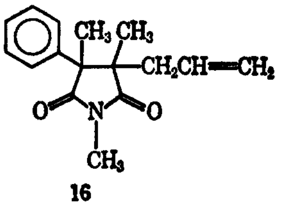
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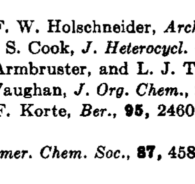
The use of NaH in THF also led to successful acylations with **3** (R = R′ = CH_3) and a variety of esters as shown in Table III. Winterfeld[11] reported that N-methylsuccinimide condensed with ethyl picolinate using sodium in benzene to gixe 90% yield of the acylation product. Seidel[12] has recently reported the acylation of N-arylpyrrolidones using alkoxides in DMF, and Zimmer[13] has used NaH in THF for the aldol condensation of aldehydes with 1-acetyl-2-pyrrolidone. Earlier, Meyer and Vaughan[14] had condensed ethyl formate with 1-phenyl-2-pyrrolidone to obtain the hydroxymethylene derivative, while Korte[15] and coworkers have studied a variety of similar condensations with pyrrolidones and piperidones. The interesting carboxylation using magnesium methyl carbonate that Finkbeiner[16] applied to 3-phenyl-2,4-oxazolidinedione was unsuccessful with **3** (R = R′ = CH_3) while condensation with diethyl carbonate gave the ester in excellent yield.

Since the structural assignments for many of the products obtained in these studies as well as the analysis of mixtures of products depended heavily on nmr data, these are tabulated in Table IV along with data for some pertinent known compounds. The marked difference in chemical shift for 3 and 4 protons in this series is immediately apparent. The highest field peak position noted for a 3 proton was 3.43 and the lowest field peak position for a 4 proton was 3.03 for only alkyl-substituted compounds. This difference along with the lack of spin–spin splittings made the assignment of structures for the 4-alkylation products relatively simple. Thus in the spectrum of the product of alkylation of **2** (R′ = C_2H_5) with ethyl bromide a sharp singlet at 3.89 was observed. Had the product been **17**, a triplet due to splitting by the adjacent methylene would have been expected near 2.6–2.8 and a second triplet due to the other possible stereoisomer would have been likely. The nmr spectrum for the derivative without the N-methyl group prepared by an unambiguous route, has been reported recently[17] and shows a singlet at 4.1. All of the succinimides prepared in this study showed typical[18] infrared absorption for such functionality except for those acylation products which existed at least partially in their enol forms (see Experimental Section). The structures of the products thus rests on a combination of elemental analysis, nmr and ir spectra and, in at least some cases, nonidentity with known compounds. The completely alkylated products (**11**) revealed a complete absence of ring protons by their nmr spectra and normal succinimide functionality by their ir spectra.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Experimental Section[19]

Starting Materials.—The phenylsuccinimides used in these studies were prepared by known methods: 4-allyl-1,3-dimethyl-3-phenylsuccinimide,[20] 4-benzyl-1-methyl-3-phenylsuccinimide,[20] 1,3-dimethyl-3-phenylsuccinimide,[21] 1,4-dimethyl-3-phenylsuccinimide,[22] 4-ethyl-3-phenylsuccinimide,[22] 4-ethyl-1-methyl-3-phenyl-1succinimide,[22] 4-ethyl-3-methyl-3-phenylsuccinimide,[23] and 1-methyl-3-phenylsuccinimide.[21]

Alkylation at the 3 Position. 1,3-Dimethyl-4-ethyl-3-phenylsuccinimide.—A solution of 21.7 g (0.10 mol) of 4-ethyl-1-methyl-3-phenylsuccinimide in 100 ml of DMF was treated portionwise under nitrogen with 5 g (0.11 mol) of 50% NaH in mineral oil. After stirring for 3 hr at 50°, the mixture was cooled and treated dropwise with 15 ml of methyl iodide (excess). After the exothermic reaction subsided, the mixture was held at 60–80° for 2 hr. After cooling, filtration and removal of solvent, the residue was dissolved in benzene and washed thrice with water. Distillation afforded 19.3 g (85%) of crude product collected at 125–130° (0.1 mm). The ir (film) and nmr ($CDCl_3$) spectra of this material were identical with those of a sample of authentic material[23] except for a small band at 1650 cm^{-1}, and a peak at 3.68 s (OCH_3) that integrated for 0.33 proton (*ca.* 10% enol ether present).

N-Benzoyl-4-ethyl-3-phenylsuccinimide.—To a solution of 101.5 g (0.50 mol) of 4-ethyl-3-phenylsuccinimide in 300 ml of pyridine was added dropwise 77.2 g (0.55 mol) of benzoyl chloride at 25–30° and the mixture stirred 1 hr longer before being heated to 55–65° for 1 additional hr. The mixture was diluted with ether, filtered, and freed of solvent. The crystalline residue recrystallized from benzene–petroleum ether (bp 30–60°) had mp 125–126° and amounted to 134 g (87%): ir (KBr) 1794 (m), 1730 (s), and 1695 cm^{-1} (m); nmr data are given in Table IV.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.26; H, 5.57. Found: C, 74.20; H, 5.61.

4-Ethyl-3-methyl-3-phenylsuccinimide.—A solution of 76.8 g (0.25 mol) of the above benzoyl derivative in 500 ml of DMF was treated portionwise with 14 g (20% excess) of 50% NaH in mineral oil at 20–25°. The dark red solution was stirred 2 hr then treated dropwise with 45 g (excess) of methyl iodide at 25–28° (intermittent cooling). After 1 hr, the mixture was heated to 55–70° for 1 additional hr, then cooled, filtered, and freed of solvent, leaving 78 g of crude product. This was dissolved in 300 ml of EtOH plus 30 ml of H_2O and treated all at once with 33 g of KOH. The solution was heated under reflux for 1.5 hr, cooled, filtered, diluted with an equal volume of water, and washed thrice with benzene. After acidification,

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(12) M. C. Seidel and R. S. Cook, *J. Heterocycl. Chem.*, **3**, 311 (1966).

(13) H. Zimmer, D. C. Armbruster, and L. J. Trauth, *ibid.*, **2**, 171 (1965).

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(15) K. H. Büchel and F. Korte, *Ber.*, **95**, 2460 (1962), and earlier papers cited therein.

(16) H. Finkbeiner, *J. Amer. Chem. Soc.*, **87**, 4588 (1965).

(17) K. Tamaribuchi, Ph.D. Thesis, Stanford, 1964.

(18) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958.

(19) Melting points were taken in open glass capillaries using a Thomas-Hoover unimelt apparatus and are uncorrected. Infrared spectra were recorded on Bechman IR-7 and IR-9 spectrophotometers. Nmr spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are quoted in parts per million downfield from tetramethylsilane (δ), and coupling constants in cycles per second.

(20) F. P. Hauck, J. Demick and J. T. Fan, *J. Med. Chem.*, **10**, 611 (1967).

(21) C. A. Miller and L. M. Long, *J. Amer. Chem. Soc.*, **73**, 4895 (1951).

(22) C. A. Miller, H. I. Scholl, and L. M. Long, *ibid.*, **73**, 5608 (1951).

(23) C. A. Miller and R. L. Hull, U. S. Patent 3,183,245 (1965).

the product was extracted with benzene, washed with bicarbonate solution, dried over $MgSO_4$ and freed of solvent. The 26 g of crude product was distilled to yield 21 g (39%) of product collected at 160–165° (0.5 mm). The ir and nmr spectra were identical with those of an authentic sample.[23]

General Procedure for Alkylation at the 4 Position of 1 and 2 Types. In Liquid Ammonia.—To a suspension of 2.0 mol of $NaNH_2$ in 2 l. of NH_3 was added a solution of 0.25 mol of the imide in 250 ml of toluene rapidly but dropwise. A yellow precipitate formed. After 10 min, the mixture was treated with 2.0 mol of halide in 500 ml of ether dropwise. After 1 hr the mixture was treated with excess NH_4Cl to decompose any remaining base, the ammonia evaporated, the inorganics removed by filtration. After removal of solvents, the products were distilled twice for analysis.

In Ether-LDIPA.—To a solution of 2.0 mol of lithium diisopropylamide in 2 l. of ether was added rapidly but dropwise a solution (0.25 mol) of the imide in 250 ml of toluene. After 10 min the dark solution containing a yellow precipitate was treated rapidly dropwise with 2.0 mol of halide in 500 ml of ether. After 0.5 hr under reflux, the mixture was cooled and treated with water. The organic layer was separated, washed with water, dried and distilled as above.

General Procedure for Dialkylations at the 4 Position of 3 with THF-NaH.—A stirred solution of 0.5 mol of the imide and at least 1.0 mol of the appropriate halide in 1 l. of THF was treated portionwise with at least 1.0 mol of NaH (mineral oil suspension). If gas evolution did not commence immediately, the mixture was heated at the beginning of the addition, before much hydride was added, until reaction had definitely started. The mixture was gradually brought to reflux and held there for 12–36 hr depending upon the reactivity of the halide employed. The mixture was then cooled, treated dropwise with 20 ml of water followed by 100 ml of acetic acid, and filtered. After removal of solvent, the residue was taken up in benzene, washed thrice with water, and again freed of solvent. When possible, the residue was triturated with petroleum ether to remove mineral oil before fractionation. In some cases, chromatography on neutral alumina was used to finish the separation from starting material when fractional distillation did not accomplish this.

Preparation of the Self-Condensation Product 14.—A solution of 203 g (1.0 mol) of **3** ($R = R' = CH_3$) and 181 g (1.3 mol) of 3-bromopropanol in 2 l. of THF was treated portionwise with 120 g of 57% NaH in mineral oil. The reaction was quite vigorous causing the temperature to rise gradually to 48° then fall slowly to *ca.* 40° during the addition. The mixture was then heated under reflux for 24 hr, cooled, and treated dropwise with 200 g of acetic acid. After filtration, the solids were washed with benzene and the combined filtrates freed of solvent. The residue was taken up in benzene, washed twice with water and again freed of solvent. Mineral oil was removed by repetitive trituration with petroleum ether, and the residue then distilled. After starting material and a small forerun, 68 g of product (35%) was collected at 255–260° (0.3 mm) and soon solidified. A sample recrystallized from acetic acid-water had mp 245–248°; ir (KBr) 1755, 1735 and 1680 cm^{-1}; nmr ($CDCl_3$) 3.56 s, 3.05 (3 H, NCH_3), 2.81 ($J = 17$ and 2.67, $J = 17$, AB pattern,[24] 2 H, ring CH_2), 1.88 (3 H), and 1.52 (3 H, CH_3).

Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.20; H, 6.23. Found: C, 74.27; H, 6.24.

General Procedure for Acylation of 3.—A solution of 1.0 mol of the imide and at least 2.0 mol of the appropriate ester in 1 l. of THF was stirred and treated with a small portion of NaH–mineral oil plus a few drops of absolute EtOH, then heated under reflux until gas evolution definitely started. Heating was stopped and the rest of 2.0 mol of NaH added portionwise at a rate to maintain vigorous but controlled refluxing. Heating was resumed and continued overnight. The mixture was cooled, treated dropwise with acetic acid, diluted with benzene, and filtered. The filtrate was taken to dryness and the residue dissolved in benzene, washed twice with water and again freed of solvent. Trituration with petroleum ether removed the mineral oil. Those products not solids at this point were distilled.

Registry No.—14, 19362-75-5.

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[24] R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 83.