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C-Alkylation of α-Amidoketones

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C-Alkylations of some N-acetonyl- and N-phenacylamides were effected with alkyl halides by means of sodium ethoxide in ethanol or potassium amide in liquid ammonia. The present paper deals with its scope and structural limitation for these alkylation reactions.

Up to the present C-alkylation with alkyl halide has been exhibited by a wide range of active methylene compounds, however, no report in chemical literature was found describing the C-alkylation of α-amidoketones. Recently some N-acetonyl- and N-phenacylamides were found to undergo C-alkylation by means of sodium ethoxide in ethanol or potassium amide in liquid ammonia. We wish to report our investigation on this alkylation reaction chiefly dealing with its scope and structural limitation.

Alkylation by Means of Sodium Ethoxide in Ethanol

Some N-acetonyl- and N-phenacyl-substituted amides have been recognized to be effective in alkylations with alkyl halides. These compounds, when treated with ethanolic sodium ethoxide solution, produced yellowish or brownish-yellow carbanion that underwent C-alkylation with appropriate halides. The alkylation reactions were processed under the

Table I. C-Alkylation[a)] of α-Amidoketones

$$RCOCH_2NHCOR' \xrightarrow[C_2H_5ONa \text{ in ethanol}]{R''X} RCOCHNHCOR' \quad (R'')$$

R	R′	R″X	Yield (%)
CH_3	CH_3	$C_6H_5CH_2Cl$	61
CH_3	CH_3	CH_2=$CHCH_2Cl$	50
CH_3	CH_3	$CH_3CH_2CH_2CH_2Br$	20
CH_3	CH_3	$(CH_3)_2CHCH_2Br$	0
CH_3	CH_3	$C_6H_5CH_2CH_2Br$	0
CH_3	C_6H_5	$C_6H_5CH_2Cl$	62
CH_3	C_6H_5	CH_2=$CHCH_2Cl$	51
C_6H_5	CH_3	$C_6H_5CH_2Cl$	90
C_6H_5	CH_3	CH_2=$CHCH_2Cl$	76
C_6H_5	CH_3	$C_6H_5CH_2CH_2Br$	17
C_6H_5	C_6H_5	$C_6H_5CH_2Cl$	95
C_6H_5	C_6H_5	CH_2=$CHCH_2Cl$	94
C_6H_5	C_6H_5	$CH_3CH_2CH_2CH_2Br$	89
C_6H_5	C_6H_5	$(CH_3)_2CHCH_2Br$	54
C_6H_5	C_6H_5	$C_6H_5CH_2CH_2Br$	18

a) The standard conditions are written in Experimental.

1) Location: *160, Oshika, Shizuoka.*

standard conditions, in which the sodio salt in ethanol was heated along with the alkyl halide at 60—65° for 6 hours. Yields are listed in Table I and data of the alkylation products are shown in Table V.

Most of the known products showed well correspondence of physical data with those reported. All the products exhibited in their infrared (IR) spectra >NH and >C=O stretching vibration bands, respectively, at 3354—3198 cm^{-1} and 1726—1686 cm^{-1}, bearing evidence of the assigned C-alkyl derivatives. The nuclear magnetic resonance (NMR) splitting patterns of C_α-H and C_β-2H observed in the spectra of representative benzylation products were well indicative of the assigned C-alkylating structures as shown in Table II, where the splitting patterns of C_β-2H of phenacyl derivatives ($R=C_6H_5$) were interpreted as ABX splitting system. Exact measurements of the other alkylation products were not possible because of complex patterns of the spectra.

Table II. Nuclear Magnetic Resonance Spectra of Type

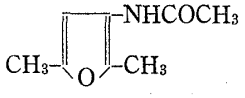
$$R\text{–}CO\text{–}\underset{\alpha}{C}H(\overset{\beta}{C}H_2\text{–}C_6H_5)\text{–}NH\text{–}CO\text{–}R'$$

R	R′	τ-Value (Multiplicity)[a] (J in cps)	
		C_α–H	C_β–2H
CH_3	CH_3	5.15 (q) (6.6)	6.93 (d) (6.6)
CH_3	C_6H_5	4.96 (q) (6.6)	6.78 (d) (6.6)
C_6H_5	CH_3	4.07 (se) (5.5, 7.2)	6.98 (q) (5.8, 13.5)
			6.63 (q) (6.0, 13.5)
C_6H_5	C_6H_5	3.93 (se) (5.5, 7.2)	6.86 (q) (5.2, 14.0)
			6.50 (q) (5.8, 14.0)

a) The following abbreviations are used: q=quartet, d=doublet, se=sextet.

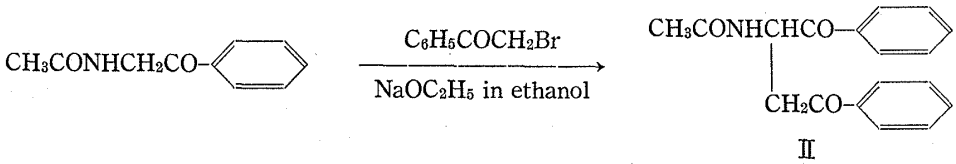
Furthermore, we were tempted to carry out the reaction with α-halo ketone in the expectation that the primarily formed β-diketone would undergo cyclization to furan nucleus. Reaction of N-acetonylacetamide with bromoacetone under the same conditions as those in the foresaid alkylation reaction resulted in the formation of N-(2,5-dimethyl-3-furyl)acetamide (I). The

$$CH_3CONHCH_2COCH_3 \xrightarrow[NaOC_2H_5 \text{ in ethanol}]{CH_3COCH_2Br}$$



I

observed NMR spectrum of this new compound was interpreted to fit the structure by the following assignments: the four singlet peaks at τ 8.14, 7.86, 7.74 and 2.97, respectively, to –$COCH_3$, –CH_3, –CH_3 and ⟩C–H. However, in a reaction of N-phenacylacetamide with phenacyl bromide we obtained open chain γ-diketone, N-(α-phenacylphenacyl)acetamide (II), as follows.



II

The NMR spectrum of this product is consistent with its structure by the following splitting patterns: the singlet at τ 8.03 to the methyl hydrogens, the doublet at τ 6.38 to the methylene hydrogens, the doublet at τ 4.10 to the methine hydrogen and the doublet at τ 2.99 to the >NH hydrogen.

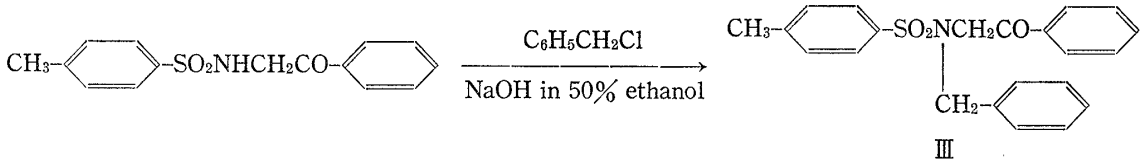
Examinations were undertaken with several α-amidoketones with variations of amide group to see effect of amide group on the alkylation reaction, benzylation being elected as standard. The results of the experiments are summarized in Table III.

Table III. Effect of Amide Group of α-Amidoketone on Benzylation

Substrate	Yield (%)	Substrate	Yield (%)
$CH_3CONHCH_2COCH_3$	61	$CH_3CO\backslash NCH_2COCH_3$ ($CH_3/$)	0
$C_6H_5CONHCH_2COCH_3$	62	$CH_3CONHCH_2COC_6H_5$	90
$CH_2(-CO\backslash)_2NCH_2COCH_3$	0	$C_6H_5CONHCH_2COC_6H_5$	95
$C_6H_4(/CO\backslash)_2NCH_2COCH_3$	0	$C_6H_4(/CO\backslash)_2NCH_2COC_6H_5$	0
$CH_3CO\backslash NCH_2COCH_3$ ($CH_3CO/$)	59	p-$CH_3C_6H_4SO_2NHCH_2COC_6H_5$	33[a]

a) Yield of N-benzyl produet. Condition: NaOH in 50%, ettanol

The following distinctions were seen in change of the amide group: 1) To see effect of tertiary amide group we examined with N-acetonyl-N-methylacetamide but almost no reaction occured in this case. 2) Succinimide- and phthalimide-substituted N-acetonyl or N-phenacyl compounds did not suffer benzylation but other reaction, which we did not investigated further. The latter phthalimide-substituted compounds have been known to afford isoquinoline derivatives by action of base.[2] The diacylsubstituted derivative, N-acetonyldiacetamide,[3] underwent benzylation resulting in the formation of N-(α-acetylphenethyl)acetamide in 59% yield with elimination of one acetyl group. The disubstituted substrate was confirmed to be labile in conversion to N-acetonylacetamide in the ethoxide-ethanol medium. Consequently, the reaction path through this N-acetonylacetamide in the above benzylation must be regarded as an intermediate course. 3) N-Phenacyl-*p*-toluenesulfonamide underwent N-benzylation to give N-benzyl-N-phenacyl-*p*-toluenesulfonamide (III), melting point of which was well in accord with that reported previously[4] and the NMR spectrum was in agreement with the structure. To carry out this N-benzylation in 50% ethanolic sodium hydroxide solution was shown to be better in yield (33%).



III

From the above limitations, it would then be presumed that in a series of α-amidoketone the type of the structure considerably effective for the alkylation in ethanolic ethoxide is indicated by $RCONHCH_2COR'$.

Alkylation by Means of Potassium Amide in Liquid Ammonia

A means of using potassium amide in liquid ammonia was adopted for alkylation of α-amidoketones with halides. Results of these experiments are shown in Table IV. All the runs were processed under uniform conditions, in which the α-amidoketone and alkyl halide were added to a liquid ammonia solution of potassium amide and the resulting mixture was

2) S. Gabriel and J. Colman, *Ber.*, **33**, 2630 (1900).
3) R.H. Wiley and O.H. Borum, *J. Am. Chem. Soc.*, **70**, 2005 (1948).
4) S. Gabriel, *Ber.*, **47**, 1336 (1914).

allowed to react at the refluxing temperature for 8 hours. This means was recognized in most cases to be more efficient in raising the yields of the alkylation products. As can be seen from Table IV, several alkyl halides other than benzyl chloride and allyl chloride showed greater efficiency for this alkylation, although they were inert or less reactive to the alkylation with ethoxide in ethanol. The alkylation products, inclusive of additional seven new compounds, were identified by elemental analyses and by noting well correspondence of their IR spectra. These data are listed in Table V.

Table IV. C-Alkylation[a] of α-Amidoketones

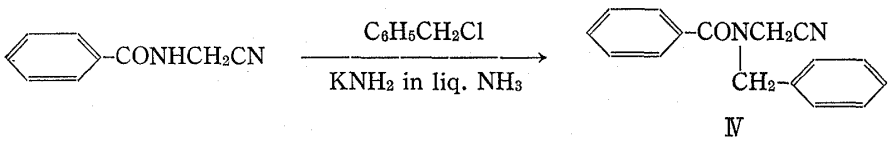
$$RCONHCH_2COR' \xrightarrow[KNH_2 \text{ in liquid ammonia}]{R''X} RCONHCHCOR' \quad (R'' \text{ on CH})$$

R	R′	R″X	Yield, %
CH_3	CH_3	$C_6H_5CH_2Cl$	92
CH_3	CH_3	CH_2=$CHCH_2Cl$	76
CH_3	CH_3	$CH_3CH_2CH_2CH_2Br$	64
CH_3	CH_3	$(CH_3)_2CHCH_2Br$	30
CH_3	CH_3	$C_6H_5CH_2CH_2Br$	16
C_6H_5	CH_3	$C_6H_5CH_2Cl$	53 (3)[b]
C_6H_5	CH_3	$CH_3CH_2CH_2CH_2Br$	14 (4)[b]
C_6H_5	CH_3	$(CH_3)_2CHCH_2Br$	14 (3)[b]
C_6H_5	CH_3	$C_6H_5CH_2CH_2Br$	19
CH_3	C_6H_5	$(CH_3)_2CHCH_2Br$	26
C_6H_5	C_6H_5	$C_6H_5CH_2Cl$	84
C_6H_5	C_6H_5	CH_2=$CHCH_2Cl$	87
C_6H_5	C_6H_5	$CH_3CH_2CH_2CH_2Br$	65
C_6H_5	C_6H_5	$(CH_3)_2CHCH_2Br$	42
C_6H_5	C_6H_5	$C_6H_5CH_2CH_2Br$	40

a) The standard conditions are written in Experimental.
b) In parentheses are described yields of the dialkylated products.

As to N-phenacylbenzamide substituent, effect of phenyl of benzamide group on alkylation was examined with variations to the representative *p*-methoxy- and *p*-nitrophenyl. N-Phenacyl-*p*-methoxybenzamide was regarded to be more reactive to C-alkylation than the parent compound, by noting increase of yield from 42% to 78% in isobutylation with isobutyl bromide. In the case of *p*-nitro substituent no isobutylation product was obtained. These facts are suggestive of facilitation by the presence of electron-releasing substituent at phenyl group.

Several other compounds, in which benzoyl group of N-phenacylbenzamide was replaced by substituents *i.e.* $-CONH_2$, $-CON(CH_3)_2$, $-CN$, were used as substrates for the alkylation reaction with the most efficient benzyl chloride, but no desirable C-benzylation product was obtained in every case. However, in the case of the last cyano substituent N-benzylation at benzamide nitrogen was shown to occur giving N-benzyl-N-cyanomethylbenzamide (IV) in 38% yield, of which NMR spectrum was interpreted to fit the structure by the following assignments: singlet at τ 5.42 to cyanomethyl protons and singlet at τ 5.72 to methylene protons of benzyl.



IV

TABLE V

1. Alkylation Products of Type $RCOCHNHCOR'$ with R''

R	R′	R″	Method[a]	Appearance (Recryst. solv.)	bp °C/mmHg	mp °C	IR ν_{max} cm^{-1} –NH–	–CO–	amide	Formula		Elemental analysis % C	H	N
CH_3	CH_3	$C_6H_5CH_2$[b]	A, B	needles (AcOEt)	143—145/0.02	96—97 (lit.[6] 96.5—97)	3328	1713	1631	$C_{12}H_{15}O_2N$	Calcd.:	70.22	7.37	6.82
											Found:	70.05	7.47	6.82
CH_3	CH_3	CH_2=$CHCH_2$	A, B	liquid	100—104/0.02		3267	1720	1650	$C_8H_{13}O_2N$	Calcd.:	61.91	8.41	9.03
											Found:	61.71	8.45	9.05
CH_3	CH_3	$CH_3CH_2CH_2CH_2$	A, B	liquid	146—149/15 (lit.[6] 115/0.015)		3280	1720	1650	$C_9H_{17}O_2N$	Calcd.:	63.13	10.00	8.18
											Found:	63.33	10.04	7.95
CH_3	CH_3	$(CH_3)_2CHCH_2$	B	liquid	131—136/7 (lit.[7] 125—127/5)		3280	1720	1650	$C_9H_{17}O_2N$	Calcd.:	63.13	10.00	8.18
											Found:	63.11	10.16	7.96
CH_3	CH_3	$C_6H_5CH_2CH_2$	B	needles ($C_2H_5)_2O$	185—187/0.6	73—74	3302	1718	1630	$C_{13}H_{17}O_2N$	Calcd.:	71.20	7.82	6.39
											Found:	71.33	7.77	6.48
CH_3	C_6H_5	$C_6H_5CH_2$[b]	A, B	prisms (EtOH)		116—117 (lit.[8] 113.5—114)	3354	1726	1625	$C_{17}H_{17}O_2N$	Calcd.:	76.38	6.41	5.24
											Found:	76.16	6.40	5.62
CH_3	C_6H_5	CH_2=$CHCH_2$	A	needles (AcOEt)	173—177/6	57—58	3256	1720	1629	$C_{13}H_{15}O_2N$	Calcd.:	71.86	6.96	6.45
											Found:	71.55	6.73	6.19
CH_3	C_6H_5	$CH_3CH_2CH_2CH_2$	B	needles ($C_2H_5)_2O$		53—54	3292	1718	1632	$C_{14}H_{19}O_2N$	Calcd.:	72.07	8.21	6.00
											Found:	71.80	8.19	5.95
CH_3	C_6H_5	$(CH_3)_2CHCH_2$	B	needles (EtOH)		65—66 (lit.[7] 69)	3324	1727	1629	$C_{14}H_{19}O_2N$	Calcd.:	72.07	8.21	6.00
											Found:	72.30	8.23	6.00
CH_3	C_6H_5	$C_6H_5CH_2CH_2$	B	needles (EtOH)		84—85	3327	1713	1629	$C_{18}H_{19}O_2N$	Calcd.:	76.84	6.81	4.98
											Found:	76.88	6.87	4.96
C_6H_5	CH_3	$C_6H_5CH_2$[b]	A	prisms (AcOEt)		87—88 (lit.[9] 107—108)	3198	1686	1641	$C_{17}H_{17}O_2N$	Calcd.:	76.38	6.41	5.24
											Found:	76.39	6.38	5.25
C_6H_5	CH_3	CH_2=$CHCH_2$	A	needles (AcOEt)	150—155/0.08	61—63	3294	1686	1637	$C_{13}H_{15}O_2N$	Calcd.:	71.86	6.96	6.45
											Found:	71.78	6.97	6.61
C_6H_5	CH_3	$(CH_3)_2CHCH_2$	B	prisms $(C_2H_5)_2O$		84—86	3277	1686	1639	$C_{14}H_{19}O_2N$	Calcd.:	72.07	8.21	6.00
											Found:	72.03	8.21	5.73
C_6H_5	CH_3	$C_6H_5CH_2CH_2$	A	needles ($(C_2H_5)_2O$–petr. ether)		65—67	3304	1684	1642	$C_{18}H_{19}O_2N$	Calcd.:	76.84	6.81	4.98
											Found:	76.43	6.78	4.94
C_6H_5	C_6H_5	$C_6H_5CH_2$[b]	A, B	needles (AcOEt)		143—144 (lit.[10] 137—138)	3311	1686	1638	$C_{22}H_{19}O_2N$	Calcd.:	80.22	5.81	4.25
											Found:	79.89	5.95	3.98
C_6H_5	C_6H_5	CH_2=$CHCH_2$	A, B	needles (EtOH)		79—80	3325	1692	1638	$C_{18}H_{17}O_2N$	Calcd.:	77.39	6.13	5.01
											Found:	77.42	6.24	4.78
C_6H_5	C_6H_5	$CH_3CH_2CH_2CH_2$	A, B	needles (EtOH)		94—95	3287	1690	1631	$C_{19}H_{21}O_2N$	Calcd.:	77.26	7.17	4.74
											Found:	77.03	7.31	4.86
C_6H_5	C_6H_5	$(CH_3)_2CHCH_2$	A, B	needles (EtOH)		108—109 (lit.[11] 110)	3287	1693	1634	$C_{19}H_{21}O_2N$	Calcd.:	77.26	7.17	4.74
											Found:	77.47	7.37	4.91
C_6H_5	C_6H_5	$C_6H_5CH_2CH_2$	A, B	prisms (EtOH)		115—116	3364	1680	1652	$C_{23}H_{21}O_2N$	Calcd.:	80.44	6.16	4.08
											Found:	80.53	5.93	3.92

2. Dialkylation Products of Type $RCOCR''NHCOR'$ with R''

R	R′	R″	Method[a]	Appearance (Recryst. solv.)	mp °C	IR ν_{max} cm^{-1} –NH–	–CO–	amide	Formulae		Elemental analysis % C	H	N
CH_3	C_6H_5	$C_6H_5CH_2$	B	plates (EtOH)	159—160	3354	1697	1642	$C_{24}H_{23}O_2N$	Calcd.:	80.64	6.49	3.92
										Found:	80.78	6.53	3.89
CH_3	C_6H_5	$CH_3CH_2CH_2CH_2$	B	plates (EtOH)	131—132	3245	1710	1624	$C_{18}H_{27}O_2N$	Calcd.:	74.70	9.40	4.84
										Found:	74.81	9.64	4.98
CH_3	C_6H_5	$(CH_3)_2CHCH_2$	B	needles (benzene–ligroin)	99—101	3224	1718	1626	$C_{18}H_{27}O_2N$	Calcd.:	74.70	9.40	4.84
										Found:	74.89	9.39	4.72

a) A: sodium ethoxide in ethanol; B: potassium amide in liquid ammonia
b) NMR data of these compounds are shown in Table II.

Experimental

Preparation of α-Amidoketones——The following six compounds used as substrates for the alkylations were prepared by previously reported methods: N-Acetonylacetamide, mp 39—40° (lit.[3] mp 39—41°),

5) G.H. Cleland and C, Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).
6) V. Franzen, *Ann.*, **602**, 199 (1957).
7) T. Toyoda, T. Suyama and S. Kanao, *Chem. Pharm. Bull.* (Tokyo), **8**, 939 (1960).
8) S. Searles and G.J. Cvejanovich, *J. Am. Chem. Soc.*, **72**, 3200 (1950).
9) T.N. Ghosh, B. Bhattacharya and S. Datta, *J. Indian Soc.*, **34**, 417 (1957).
10) H. Zinner and G. Brossmann, *J. Prakt. Chem.*, (4)**5**, 91 (1957).
11) K. Yamamoto and K. Karigome, *Yakugaku Zasshi*, **75**, 1222 (1955).

N-acetonyldiacetamide, bp 143—147° (15 mmHg) (lit.[3] bp 105—108° (2 mmHg)), N-acetonylbenzamide, mp 82—84° (lit.[12] mp 84°), N-acetonylphthalimide, mp 122—123° (lit.[13] mp 124°), N-phenacylacetamide, mp 86—87° (lit.[14] mp 87°), N-phenacylbenzamide, mp 121—122° (lit.[15] mp 122°). N-Acetonyl-N-methylacetamide, N-phenacyl-*p*-anisamide and N-phenacyl-*p*-toluenesulfonamide were prepared by other than previously reported methods and N-acetonylsuccinimide, N-phenacylphthalimide and N-phenacyl-*p*-nitrobenzamide were newly prepared in the present work. Details are described in the following.

N-Acetonyl-N-methylacetamide——A mixture of 7 g (0.042 mole) of methylaminoacetone ethylene ketal hydrochloride[16] and 50 ml of 5% hydrochloric acid was refluxed for 1.5 hr. After evaporation to dryness under reduced pressure, 35 ml of acetic anhydride and 3 g of anhydrous sodium acetate were added to the residue and the mixture was refluxed for 1.5 hr. An excess of acetic anhydride was removed under reduced pressure and the residue was extracted with ether. The ethereal solution was dried over K_2CO_3. The ether was evaporated and the residue was distilled to give colorless liquid, bp 97—99° (0.1 mmHg) (lit.[17] bp 101—103° (2mmHg)), weighing 4.55 g (84%). IR ν_{max}^{liq} cm^{-1}: 1728 (>C=O), 1650 (amide). NMR (10% in $CDCl_3$) τ: 7.90 (6H, singlet $2CH_3$–CO), 6.97 (3H, singlet, CH_3–N<), 5.85 (2H, singlet, $-CH_2-$). 4-Nitrophenylhydrazone: *Anal.* Calcd. for $C_{11}H_7O_3N_3$: C, 54.55; H, 6.10; N, 21.20. Found: C, 54.93; H, 6.03; N, 21.58.

N-Phenacyl-*p*-anisamide——To a mixture of 15 ml of water, 1.5 g of Na_2CO_3 and 5 g (0.0293 mole) of *p*-anisoyl chloride were added alternately in small portions a solution of 4.4 g (0.0258 mole) of phenacylamine hydrochloride in 10 ml of water and a solution of 1.5 g of Na_2CO_3 in 10 ml of water at 0—10°. After additional 2 hr's stirring at room temperature, deposited crystals were collected by filtration and the filtrate was extracted with benzene. The benzene was removed under reduced pressure. The resulting crystals combined with the crystals obtained in the above were recrystallized from ethanol to colorless plates, mp 139—140° (lit.[18] mp 141°). Yield, 4.4 g (63%). IR ν_{max}^{KBr} cm^{-1}: 3380 (>NH), 1683 (>C=O), 1625 (amide), 1246, 1211, 1179, 759.

N-Phenacyl-*p*-toluenesulfonamide——In a solution of 37 g (0.45 mole) of anhydrous sodium acetate in 700 ml of 70% ethanol was in part dissolved 69 g (0.36 mole) of *p*-toluenesulfonyl chloride. To the thoroughly stirred mixture a solution of 52 g (0.3 mole) of phenacylamine hydrochloride in 200 ml of 70% ethanol and 37 g (0.45 mole) of sodium bicarbonate were added one after the other in small portion at about 5°. After the addition the stirring was continued further for 3 hr at room temperature. The resulting precipitates were collected by filtration and washed with water. Recrystallization from ethanol gave 37 g (43%) of colorless needles, mp 114—116° (lit.[4] mp 116—117°). *Anal.* Calcd. for $C_{15}H_{15}O_3NS$: C, 62.26; H, 5.23; N, 4.84; S, 11.08. Found: C, 62.52; H, 5.19; N, 4.51; S, 10.89. IR ν_{max}^{KBr} cm^{-1}: 3126 (>NH), 1704 (>C=O), 1338 ($>SO_2$), 844, 818, 759 (Ph).

N-Acetonylsuccinimide——To a solution of 2.5 g (0.025 mole) of succinimide and 3.5 g (0.025 mole) of bromoacetone dissolved in 30 ml of abst. acetone, 2.7 g of anhydrous K_2CO_3 was added and the mixture was refluxed on a water bath for 2 hr with stirring. After filtration, concentration under reduced pressure and addition of isopropyl ether to the residue gave the crystalline product, which was recrystallized from acetone–isopropyl ether to give colorless needles, mp 95—96°. Yield, 2.5 g (64%). *Anal.* Calcd. for $C_7H_9O_3N$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.16; H, 5.66; N, 9.12. IR ν_{max}^{KBr} cm^{-1}: 1730, 1700 (>C=O), 1423, 1183.

N-Phenacylphthalimide——An intimate mixture of 30 g (0.162 mole) of powdered potassium phthalimide and 36 g (0.181 mole) of bromoacetophenone was gently heated. When the exothermic reaction began, the heating was ceased. The resulting solid was recrystallized from water to give colorless needles, mp 166—167°. Yield, 30.5 g (69%). *Anal.* Calcd. for $C_{16}H_{11}O_3N$: C, 72.44; H, 4.18; N, 5.28. Found: C, 71.98; H, 4.24; N, 5.26. IR ν_{max}^{KBr} cm^{-1}: 1695 (>C=O), 758, 717 (Ph).

N-Phenacyl-*p*-nitrobenzamide——To a mixture of 33.6 g (0.196 mole) of phenacylamine hydrochloride, 250 ml of glacial acetic acid and 33.8 g of anhydrous sodium acetate was added 40 g (0.216 mole) of *p*-nitrobenzoyl chloride at 70—80° spending 0.5 hr. After additional 1 hr's stirring at 70—80°, the mixture was allowed to stand at room temperature. The resulting crytals were collected by filtration and recrystallized from ethanol to give pale yellow needles, mp 195—196°. Yield, 33.1 g (60%). *Anal.* Calcd. for $C_{15}H_{12}O_4N_2$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.53; H, 4.26; N, 10.01. IR ν_{max}^{KBr} cm^{-1}: 3370 (>NH), 1670 (>C=O), 1623 (amide), 1359, 1213 ($-NO_2$), 764, 724 (Ph).

C-Alkylation by Means of Sodium Ethoxide in Ethanol——General Procedure: To a sodium ethoxide solution prepared from 1.27 g (0.055 g atom) of sodium and 35 ml of ethanol was added 0.05 mole each of N-acetonyl- or N-phenacylamide with stirring, whereupon was obtained the solution (in the runs with N-

12) L.P. Ellinger and A.A. Goldberg, *J. Chem. Soc.*, **1949**, 263.
13) R.E. Lancaster, Jr. and C.A. Van der Werf, *J. Org. Chem.*, **23**, 1208 (1958).
14) M. Nagawa, R. Myokei and Y. Matsuse, *Takamine Kenkyujo Nenpo*, **8**, 22 (1956).
15) N.A. Adrova, M.M. Koton and F.S. Florinskii, *C.A.*, **51**, 15489 (1957).
16) E.J. Fornefeld and E.C. Kornfeld, U.S., 2,864,822, Dec. 16, 1958.
17) R.H. Wiley and O.H. Borum, *J. Am. Chem. Soc.*, **72**, 1626 (1950).
18) J. Lister and R. Robinson, *C.A.*, **7**, 327 (1914).

acetonylamides) or the suspension (in the runs with N-phenacylamides) of the yellow or brownish-yellow carbanion. After a while, to this 0.057 mole of the given alkyl halide was added and the mixture was heated at 60—65° with stirring for 6 hr. After the reaction, NaCl deposited in the reaction solution was filtered off. The filtrate was concentrated under reduced pressure to give the residue containing the alkylation product, which was isolated and purified as usual.

The reaction of N-phenacylbenzamide with benzyl chloride formed an exception to the above procedure. In this case the forming benzylation product was deposited in the reaction mixture along with NaCl. Benzene was added to the mixture so as to dissolve the product. Then, filtration and concentration followed.

Yields of the C-alkylation products obtained by the above procedures are listed in Table I and their properties and analytical data are recorded in Table V.

C-Alkylation by Means of Potassium Amide in Liquid Ammonia——General Procedure: To a colorless solution of potassium amide in liquid ammonia prepared from 2.15 g (0.055 g atom) of potassium, catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ and 100 ml of liquid ammonia was added 0.05 mole each of N-acetonyl- or N-phenacylamide with stirring, whereupon was obtained the suspension of the yellow or orange carbanion. After a while, to this a solution of 0.055 mole of the given alkyl halide in 20 ml of ether was added and the mixture was refluxed (bp of the liquid ammonia −33°) with stirring for 8 hr. After addition of 1.5 g of ammonium chloride the liquid ammonia was vented. The residue was extracted with $CHCl_3$ and the chloroform solution was dried over $MgSO_4$. The alkylation product was isolated and purified as usual.

In the case of the alkylation of N-acetonylbenzamide 3—4% of dialkylated product and 14—17% of benzamide were also obtained as by-products. And in the case of the alkylation of N-phenacylbenzamide 12—13% of benzoic acid was by-produced.

Yields of the C-alkylation products obtained by the above procedures are listed in Table IV and their properties and analytical data are recorded in Table V.

N-(2,5-Dimethyl-3-furyl)acetamide (I)——Obtained from N-acetonylacetamide and bromoacetone by the same procedure as described in the foregoing ethoxide-ethanol method as a solid distillate, bp 117—122° (0.01 mmHg). Yield, 20%. Recrystallization from ethyl acetate gave colorless needles, mp 120—121.5°. Resinified on exposure to air for a month. Positive to pine-HCl test and Liebermann test. *Anal.* Calcd. for $C_8H_{11}O_2N$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.51; H, 7.28; N, 9.11. IR ν_{max}^{KBr} cm^{-1}: 3200 (>NH), 1660 (amide), 810, 760, 750. NMR (10% in $CDCl_3$) τ: 8.14 (3H, singlet, CH_3–CO–), 7.86 (3H, singlet, CH_3–), 7.74 (3H, singlet, CH_3–), 2.97 (1H, singlet, >–H).

N-(α-Phenacylphenacyl)acetamide (II)——Obtained by the same procedure as described in the foregoing ethoxide-ethanol method from N-phenacylacetamide and bromoacetophenone by silica gel column chromatography with $CHCl_3$ as an eluent. Yield, 13%. mp 101—102° (prisms from AcOEt–iso-Pr_2O). *Anal.* Calcd. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.19; H, 5.87; N, 4.73. IR ν_{max}^{KBr} cm^{-1}: 3385 (>NH), 1672 (>C=O), 776, 748, 715, 697 (Ph). NMR (7% in $CDCl_3$) τ: 8.03 (3H, singlet, CH_3–), 6.38 (2H, doublet, J=4.2 cps, –CH_2–), 4.10 (1H, sextet, J=4.2 cps, J=8.2 cps, –CH<), 2.99 (1H, doublet, J=8.2 cps, >NH), 2.8—2.0 (10H, multiplet, aromatic).

N-Benzyl-N-phenacyl-*p*-toluenesulfonamide (III)——To a mixture of 60 ml of ethanol, 60 ml of H_2O and 27 ml (0.033 mole) of 5% NaOH was added 8.7 g (0.03 mole) of N-phenacyl-*p*-toluenesulfonamide with stirring, whereupon obtained the pale yellow solution. After a while, 4.6 g (0.036 mole) of benzyl chloride was added and the mixture was stirred at 25—30° for 5 hr. The reaction mixture was allowed to stand in a refrigerator over night and the precipitates were filtered on suction. The precipitates were well washed with 5% diethylamine and recrystallized from ethanol to give colorless needles, mp 116—117° (lit.[4] 116—116.5°). Yield, 33%. *Anal.* Calcd. for $C_{22}H_{21}O_3NS$: C, 69.63; H, 5.58; N, 3.69; S, 8.45. Found: C, 69.30; H, 5.45; N, 3.48; S, 8.41. IR ν_{max}^{KBr} cm^{-1}: 1685 (>C=O), 1328, 1158 (>SO_2), 755, 730, 671 (Ph). NMR (10% in $CDCl_3$) τ: 7.58 (3H, singlet, CH_3–), 5.48 (2H, singlet, –CH_2–), 5.40 (2H, singlet, –CH_2–), 2.8—2.1 (14H, multiplet, aromatic).

N-Benzyl-N-cyanomethylbenzamide (IV)——Obtained by the same procedure as described in the foregoing potassium amide-liquid ammonia method from N-cyanomethylbenzamide and benzyl chloride by silica gel column chromatography with benzene as a solvent. Yield, 38%. Prisms (ether–petr. ether), mp 57—59°. *Anal.* Calcd. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.86; H, 5.65; N, 10.93. IR ν_{max}^{KBr} cm^{-1}: 1638 (amide), 1423, 703 (Ph). NMR (10% in $CDCl_3$) τ: 5.72 (2H, singlet, –CH_2–), 5.24 (2H, singlet, –CH_2–), 2.7—2.3 (10H, multiplet, aromatic).

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