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On the "Second Alkylation" at the α-Position of Some N,N-disubstituted Arylacetic Acid Amides

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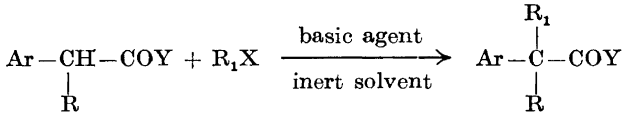
The authors have previously given a survey of the alkylation at the α-position of N,N-disubstituted arylacetic acid amides by using sodamide as basic agent and toluene or benzene as inert solvents. In this paper we report some of the results from our investigation of the introduction of a second substituent at the α-position by means of alkylation, a procedure which we briefly call the second alkylation. In contrast to the first alkylation, the second one is less general as to its application and practical use. The mobility of the remaining α-hydrogen seems to vary definitely with the group introduced during the first alkylation. In all probability also steric effects are involved in and complicate the alkylation reaction. Some of the parent α-substituted amides proved to be somewhat unstable against the basic agent when treated with it alone in toluene or when the alkylation procedure was carried out. The use of phenylsodium as salt forming agent in most cases did not improve the method.

It is known [1–4] that N,N-disubstituted diphenylacetic acid amides can be alkylated at the α-position by the simple method of using sodamide or lithium amide as basic agent in the presence of an inert solvent such as toluene or benzene. This procedure is often carried out so that the diphenylacetic acid amide (when no confusion can arise, we omit the epithet N,N-disubstituted) first is more or less completely converted to its alkali metal compound by heating with the alkali metal amide in the inert solvent. The appropriate alkylating agent is then added and the mixture is refluxed for some hours. Actually the amides of diphenylacetic acid react fairly easily with ordinary, commercial, ground sodamide. The activation of the α-hydrogen is fairly pronounced in these compounds, since, in addition to the amide group, not less than two phenyl groups contribute to the activation. The present authors [5] have recently given an account of the application of the same substitution method to many simple arylacetic acid amides. In this case, in addition to the amide group, only one aryl group (phenyl, 1-naphthyl or 3-phenanthryl) contributes to the activation of the α-hydrogen. We have also shown [6] that the method can be used in alkylation of at least some N,N-disubstituted toluene-(α)sulphonamides and diphenylmethane(α)sulphonamides.

In this paper we intend to collect the main results of our investigation of the alkylation reaction



$$\mathrm{Ar-\underset{\displaystyle R}{\underset{|}{C}H}-COY + R_1X \xrightarrow[\text{inert solvent}]{\text{basic agent}} Ar-\overset{\displaystyle R_1}{\overset{|}{\underset{\displaystyle R}{\underset{|}{C}}}}-COY}$$

where Ar is an aryl group (mostly phenyl), R is a group (actually ethyl, 2,2-dimethylbutyl, *cyclo*hexyl, allyl, benzyl, 2-pyridyl, 2-thenyl or 2-thiazolyl) which has been (or can be) introduced by the alkylation procedure described by us earlier, R_1 is the alkyl or other group which we intend to introduce in this step, and X is halogen (mostly chlorine). In our investigation, Y in the carbonamide group is a dimethylamino, diethylamino, di*iso*propylamino, *n*-propylbenzylamino, pyrrolidino, piperidino or morpholino group. The diphenyl case (Ar = R = phenyl) is excluded as sufficiently known by other investigations. Since, as pointed out above, the parent amides used in this alkylation reaction can be prepared by alkylation, in order to be brief, we call the alkylation reaction we intend to treat in this paper the second alkylation. The second alkylation is less general as to its practical application than the first one, the yields often are considerably lower and side-reactions may in some cases be important. In some cases where the conventional sodamide procedure has failed to work out satisfactorily (yields of expected substitution product lower than 40 %) we have tried phenylsodium as salt forming agent. Also potassium amide in liquid ammonia has been used. Since this last, more laborious method did not prove to give definitely better results, we did not apply it in more than one case (the alkylation of α-benzyl-phenylacetic acid benzyl-propyl-amide). These efforts will be commented on below.

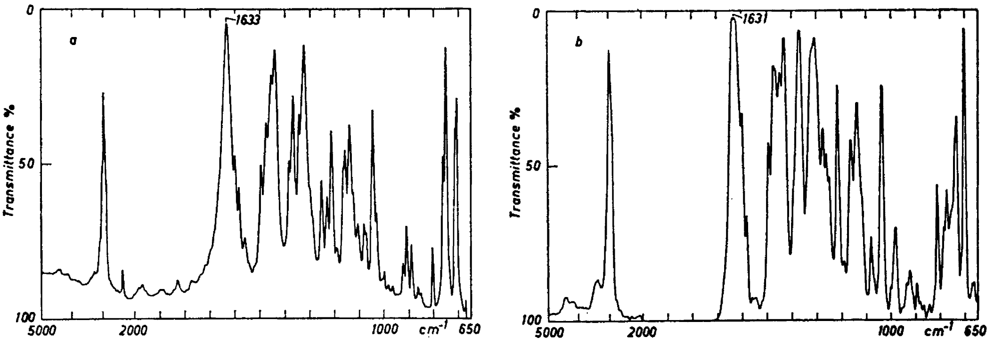


Fig. 1. Infrared spectrum of the parent amide, ethylphenylacetic acid N,N-di*iso*propylamide (a) and its α-(3,3-dimethylbutyl) derivative (b), showing that the frequency and intensity of the C=O bond of the amide group at about 1 630 $\mathrm{cm^{-1}}$ remain practically unchanged. All spectra are drawn with KBr pellet technique on a Unicam SP 100 IR instrument. The experimental error is ± 2 $\mathrm{cm^{-1}}$.

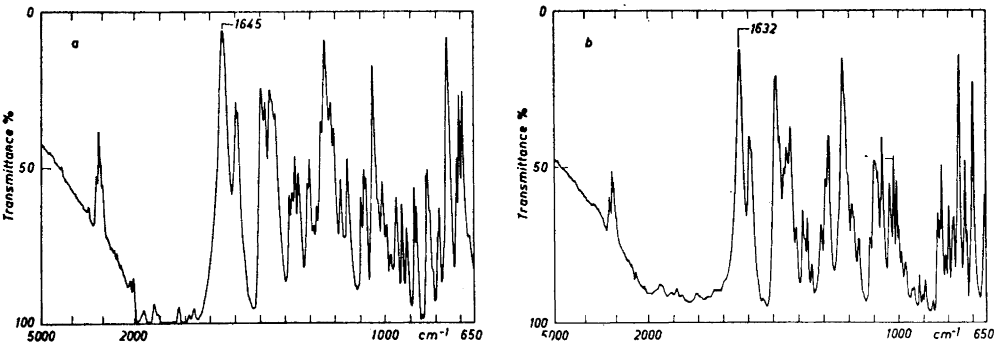


Fig. 2. Infrared spectrum of the parent amide, α-phenoxy-phenylacetic acid N,N-diethylamide (a), and its α-(*p*-chlorobenzyl) derivative (b), showing, that frequency and intensity of the C=O bond (at about 1 640 cm^{-1}) remain almost unchanged. All spectra are drawn with KBr technique on a Unicam SP 100 IR instrument. The experimental error is ± 2 cm^{-1}.

Some tentative efforts have also been made to extend the alkylation method to cases in which R is connected with the α-carbon atom *via* a heteroatom (N or O). The results of these efforts will be mentioned in the last chapter.

When substitution takes place, the reaction, as expected, leads to an alkylation at the α-carbon atom. This is indicated by the fact that the frequency and the intensity of the C=O bond of the amide group are practically unchanged after alkylation. In Figs. 1—3 the infrared spectra of three parent amides can be compared with alkylated compounds derived from them. Figs. 2 and 3 include the cases when R is phenoxy and diethylamino groups, respectively. Moreover, acid hydrolysis and decarboxylation of, for example, the expected compound γ-dimethylamino-α-(*p*-chlorophenyl)-α-(2′-pyridyl)-butyric acid di-

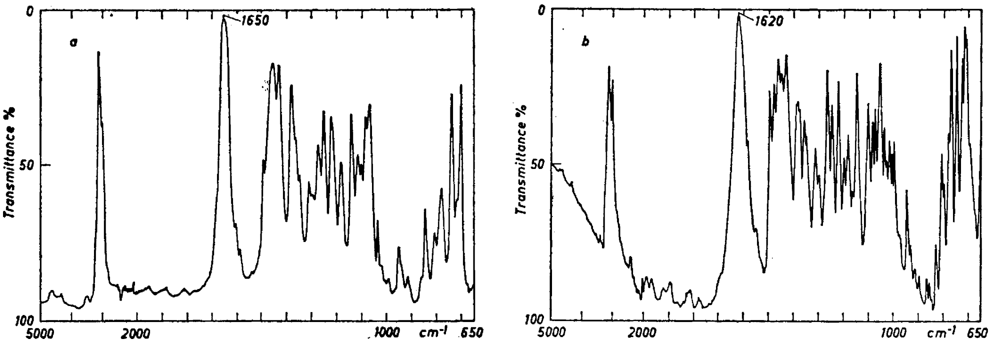


Fig. 3. Infrared spectrum of the parent amide, α-(diethylamino)-phenylacetic acid N,N-diethylamide (a), and its α-benzyl derivative (b), showing, that frequency and intensity of the C=O bond (at about 1 650 cm^{-1}) remain almost unchanged. All spectra are drawn with KBr pellet technique on a Unicam SP 100 IR instrument. The experimental error is ± 2 cm^{-1}.

methylamide gives 1-dimethylamino-3-(*p*-chlorophenyl)-3-(2′-pyridyl)-propane in excellent yield.

Tentative efforts indicate that, in contrast to the parent amides, the amide group of the alkylated products cannot be reduced by lithium aluminium hydride. This behaviour is to be expected, since there remains no hydrogen at the *a*-position (or at the amide nitrogen).

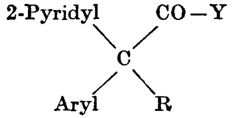
As mentioned earlier by us, in most cases the introduction of a second *a*-substituent in the arylacetic acid amides (the general discussion below is confined to phenylacetic acid amides, *i.e.* with Ar = phenyl), is more difficult than the introduction of the first one. Exceptions are formed by those cases where the earlier introduction of R includes an increase in the activation of the remaining *a*-hydrogen. When R is, for example, ethyl, *cyclo*hexyl or benzyl the reactivity against sodamide in toluene is definitely less than for the parent phenyl acetic acid amides, and it seems as if phenylsodium is to be preferred to sodamide in some of these cases (see below). The amides of phenyl-(2-pyridyl)-acetic acid form a group of compounds which can be advantageously alkylated by using sodamide (Table 1). Their sodium salts generally precipitate during their formation in boiling toluene. They react easily with tertiary 2-aminoethyl chlorides[7] but fairly slowly with ordinary alkyl chlorides. It seems as if bromides are to be preferred unless the alkylating halide is very reactive. Then the corresponding chloride can be used. The mobility of the *a*-hydrogen of these amides is at least as great as in the corresponding amides of diphenylacetic acid. That such is the case is not surprising, since the methyl hydrogen of 2-picoline is already highly active as is well known from the use of picolyllithium in synthetic work. However, too detailed conclusions about the reactivity of the amides against ordinary, commercial sodamide must not be drawn. The particle size of the ground sodamide may vary from one experiment to another, for example due to layer formation in the vessel in which the sodamide is preserved. Corrosion of the surface of the particles due to moisture during even short air exposure may decrease the reactivity even when it is stoichiometrically unimportant.

The dependence of Y of the amide group on the alkylation is more difficult to survey. Judging from the case where R = 2-pyridyl, we tentatively assume that the influence of the amide group is mainly steric, which means that amides of phenyl-(2-pyridyl)-acetic acid can be alkylated fairly independent of the nature of the substituents of the amide group, provided that R_1 is not too bulky. This is in agreement with our experience from the first alkylation procedure, in which case the substituents of the amide group are of minor importance for the applicability of the method.

From the above it follows, that when one intends to replace the two *a*-hydrogen atoms of an arylacetic acid amide, it is not unimportant in what order one tries to introduce the two groups. It seems to be a general rule, that the strongest activating (or least desactivating) group should be introduced first in order to secure a sufficient mobility of the remaining *a*-hydrogen atom for the next alkylation step.

The phenylsodium method has some advantages. Provided that the amide is stable against strong basic agents, it gives a more complete and rapid salt formation at a lower temperature than the conventional sodamide procedure.

Table 1. Compounds prepared by the "second alkylation" at the α-position of N,N-disubstituted phenyl-(2-pyridyl)-acetic acid amides *.



$$\begin{matrix} \text{2-Pyridyl} & & \text{CO}-\text{Y} \\ & \text{C} & \\ \text{Aryl} & & \text{R} \end{matrix}$$

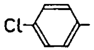
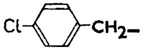
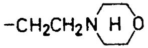
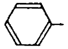
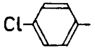
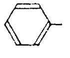
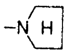
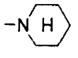
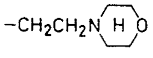
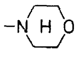
Aryl	Y	R	Yield %	B.p.°C/mm Hg M.p.°C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
	$-N(CH_3)_2$		62.5	134 −135 [d]	$C_{22}H_{20}Cl_2N_2O$	66.17	5.05	7.02	65.80	4.91	6.96
— " —	— " —		50	125 −126.5 [ab]	$C_{21}H_{26}ClN_3O_2$	65.02	6.76	10.83	64.98	6.80	10.70
— " —	— " —	$-CH_2CH_2N(CH_3)_2$	65	177 −180/0.2	$C_{19}H_{24}ClN_3O$	65.98	6.99	12.15	65.62	6.91	12.11
	$-N(C_2H_5)_2$	— " —	73	183 −188/0.5							
				80 − 82 [b]	$C_{21}H_{29}N_3O$	74.30	8.61	12.38	74.30	8.60	12.40
	— " —	— " —	62	190 −194/0.2							
			25	86 − 88 [c]	$C_{21}H_{28}ClN_3O$	67.45	7.55	11.24	67.48	7.65	11.03

Table 1. Continued.

Aryl	Y	R	Yield %	B.p.°C/mm Hg M.p. °C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2N(C_2H_5)_2$	61 44	170 —172/0.2 66.5— 67.5 [b]	$C_{25}H_{37}N_3O$	75.90	9.43	10.62	75.83	9.57	10.56
— " —		$-CH_2CH_2N(CH_3)_2$	72 40	84 — 87 93.5— 95 [e]	$C_{21}H_{27}N_3O$	74.74	8.07	12.45	74.91	8.07	12.59
— " —			55 32	220 —227/0.2 89 — 91.5[ab]	$C_{24}H_{31}N_3O_2$	73.25	7.94	10.68	73.52	7.96	10.54
— " —	— " —	— " — ,HCl		187— 88.5							
— " —		$-CH_2CH_2N(C_2H_5)_2$	65	205 —207/0.3	$C_{23}H_{31}N_3O_2$	72.41	8.19	11.01	72.14	8.00	10.85

* Method I has been applied. The yields are the total ones and refer to the parent amide. When more than one yield figure is given, the compound prepared has been further purified by recrystallization. — Melting points and boiling points are uncorrected. The former have been read from short normal thermometers covering intervals of 50°. The alkylations have been carried out with 0.1—0.05 mole of parent amide. Unless otherwise stated, X in the compound RX is chlorine.

a—e) Recrystallization from a) benzene; b) petroleum ether; ab) a mixture of benzene and petroleum ether; c) *cyclo*hexane; bc) a mixture of *cyclo*hexane and petroleum ether; d) methanol; e) acetone.

Table 2. Compounds prepared by the "second alkylation" at the α-position of some N,N-disubstituted aryl acetic acid amides.

$$\begin{matrix}\text{Ar}\\ \text{R}\end{matrix}>\text{C}<\begin{matrix}\text{R}_1\\ \text{CO-Y}\end{matrix}$$

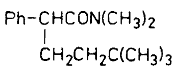
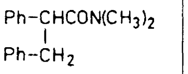
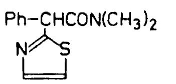
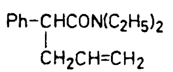
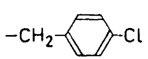
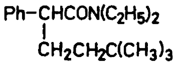
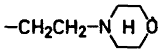
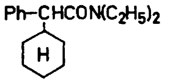
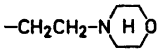
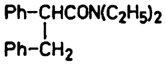
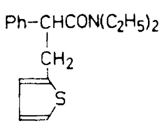
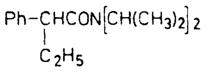
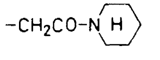
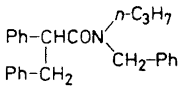
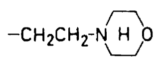
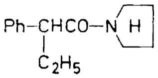
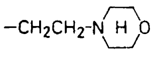
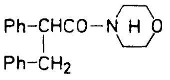
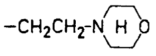
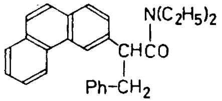
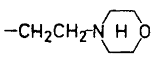
Parent amide	R$_1$	Method	Yield %	B.p.°C/mm Hg M.p.°C	Formula	Analyses Calc. C	Analyses Calc. H	Analyses Calc. N	Analyses Found C	Analyses Found H	Analyses Found N
 $\text{Ph-}\underset{\text{CH}_2\text{CH}_2\text{C(CH}_3)_3}{\underset{\vert}{\text{C}}}\text{HCON(CH}_3)_2$	$-CH_2CH_2CH_2N(C_2H_5)_2$	I II	17 47	136 −138/0.05 146 −150/0.1	$C_{23}H_{40}N_2O$	76.61	11.18	7.77	76.88	11.13	7.46
 $\text{Ph-}\underset{\text{Ph-CH}_2}{\underset{\vert}{\text{C}}}\text{HCON(CH}_3)_2$	$-CH_2CH_2N(CH_3)_2$	I II	39 24 32	165 −170/0.3 92 − 93 ^{b} 89 − 92	$C_{21}H_{28}N_2O$	77.73	8.70	8.64	77.85	8.76	8.64
	$-CH_2CH_2CH_2N[CH(CH_3)_2]_2$	I	31 15	ca 65 75 − 77 ^{bc}	$C_{22}H_{33}N_3OS$	68.17	8.58	10.84	67.80	8.40	10.78
 $\text{Ph-}\underset{\text{CH}_2\text{CH=CH}_2}{\underset{\vert}{\text{C}}}\text{HCON(C}_2\text{H}_5)_2$	$-CH_2CH_2C(CH_3)_3$	I	41	130 −135/0.2	$C_{21}H_{33}NO$	79.94	10.55	4.44	80.09	10.64	4.59
— ll —		I	76	165 −167/0.1	$C_{22}H_{26}ClNO$	74.24	7.36	3.94	74.37	7.29	3.95
— ll —	$-CH_2CH_2N(CH_3)_2$	I	64	124 −130/0.15	$C_{19}H_{30}N_2O$	75.45	10.00	9.26	74.65	10.00	9.23

Table 2. Continued.

Parent amide	R_1	Method	Yield %	B.p.°C/mm Hg M.p.°C	Formula	Analyses Calc. C	Analyses Calc. H	Analyses Calc. N	Analyses Found C	Analyses Found H	Analyses Found N
— II —	$-CH_2CH_2CH_2N(C_2H_5)_2$	I	57	170 —174/0.4	$C_{22}H_{36}N_2O$	76.69	10.53	8.13	76.12	10.55	8.20
 $\underset{CH_2CH_2C(CH_3)_3}{Ph-CHCON(C_2H_5)_2}$	$-CH_2CH_2N(CH_3)_2$	I	54	140 —142/0.2	$C_{22}H_{38}N_2O$	76.22	11.05	8.08	76.13	11.03	8.13
— II —		I II	19 25 13	168 —173/0.05 172 —178/0.1 86 — 89 b	$C_{24}H_{40}N_2O_2$	74.18	10.38	7.21	74.04	10.15	7.31
		I	15	117 —118 b	$C_{24}H_{38}N_2O_2$	74.56	9.91	7.25	74.31	9.92	7.38
 $\underset{Ph-CH_2}{Ph-CHCON(C_2H_5)_2}$	$-CH_2CH_2N(C_2H_5)_2$	I	62	190 —205/0.5	$C_{25}H_{36}N_2O$	78.90	9.54	7.36	78.82	9.20	7.14
	$-CH_2CH_2N(CH_3)_2$	I II	14 25 21	77.5— 79.0 70 — 73 76 — 78 b	$C_{21}H_{30}N_2OS$	70.35	8.43	7.82	70.11	8.44	7.51

Parent amide	R_1	Method	Yield %	B.p.°C/mm Hg M.p.°C	Formula	Analyses					
						Calc.			Found		
						C	H	N	C	H	N
 $Ph\text{-}\underset{C_2H_5}{CH}CON[CH(CH_3)_2]_2$	$-CH_2CH_2C(CH_3)_3$	I	50	125 −127/0.1	$C_{22}H_{37}NO$	79.70	11.25	4.23	79.47	10.87	4.35
— " —	$-CH_2CH_2N(C_2H_5)_2$	I	58	153 −155/0.8	$C_{22}H_{38}N_2O$	76.24	11.05	8.09	75.89	11.03	8.19
— " —		I	16 5	200 −210/0.5 125.5−127.0^{ab}	$C_{23}H_{36}N_2O_2$	74.15	9.74	7.52	74.40	9.60	7.57
		KNH_2 in liq. NH_3	48	122 −136							
			24	137.5−139.0 ^{c}	$C_{31}H_{38}N_2O_2$	79.11	8.14	5.95	79.09	8.23	6.12
		I	34 30	135 −138 ^{c} 138.5−140							
		I	23	185 −187/0.2	$C_{20}H_{30}N_2O_2$	72.69	9.15	8.48	72.66	9.12	8.63
		I	34	138 −139.5 ^{c}	$C_{25}H_{32}N_2O_3$	73.50	7.90	6.86	73.85	7.89	6.85
		I	52	165 −168.5 ^{d}							
			40	170.5−171.5	$C_{33}H_{39}N_2O_2$	79.96	7.93	5.65	80.16	7.86	5.66

Notes: Method I refers to the sodamide method; method II to the phenylsodium method. The yields are the total ones and refer to the parent amide. When more than one yield figure is given under a certain method the compound prepared according to this method has been further purified by recrystallization. — Melting points and boiling points are uncorrected. The former have been read from short normal thermometers covering intervals of 50°. With a few exceptions the alkylations have been carried out with 0.1 −0.05 mole of parent amide. Unless otherwise stated, X in the compound RX is chlorine. — a−e) Recrystallization from a) benzene; b) petroleum ether; ab) a mixture of benzene and petroleum ether; c) *cyclo*hexane; bc) a mixture of *cyclo*hexane and petroleum ether; d) methanol; e) acetone.

Reaction which may occur between the more reactive halides and the sodamide can thus be avoided. On the other hand, the preparation of phenylsodium involves a further step in the alkylation procedure. The transference of small amounts (0.05—0.1 mole) from one vessel to another involves some difficulties apart from the generally hazardous properties associated with the suspensions of phenylsodium.

In addition to the mobility of the α-hydrogen, steric factors probably are of importance. As mentioned above, bulky groups in at least two of the variables R, Y and R_1 appear to decrease the practical applicability of the method. In several cases, side-reactions have proved to occur and may predominate with low or almost no yield of the expected substitution product. To some extent these undesired results can be explained by the fact that some of the parent amides may be more or less unstable against a mere refluxing with sodamide in toluene. Thus, from the reaction mixture of 0.05 mole of the morpholide of phenylethylacetic acid (which belongs to those amides which proved to be difficult to alkylate), refluxed with sodamide for 4.5 h, only a very small amount of the morpholide could be recovered, but 42 % of a compound with the boiling point of propylbenzene could be isolated. Several of the dimethylamides show a definite tendency to split off the dimethylamide group during the alkylation procedure. This is the case when either sodamide or phenylsodium is used in the salt formation step, and the side-reaction seems to be very pronounced in some cases. When *neo*hexylphenylacetic acid dimethylamide (0.1 mole) was alkylated with 3-dimethylaminopropyl chloride and with sodamide as basic agent, the yield of α-substitution product was only 17 %. From the non-basic part of the reaction mixture, *neo*heptylbenzene and the parent amide could be isolated in yields of 48 % and 10 %, respectively. When phenylsodium was used the corresponding amounts were 47 %, 25 % and 5 % (0.1 mole of amide used). Since mere refluxing of the parent dimethylamide (0.05 mole) with sodamide in toluene for 5 h gives only traces of any product with the distillation temperature of *neo*heptylbenzene and since 66 % of dimethylamide could be recovered, it seems that, at least in this case, the cleavage of the parent amide is more pronounced when the alkylating agent is present. In the same way, benzylphenylacetic acid dimethylamide (0.6 mole) by alkylation with 2-dimethylaminoethyl chloride gave 39 % of the expected α-substitution product, 36.5 % of 1,2-diphenylethane and 14.5 % of recovered dimethylamide. In the phenylsodium case (with 0.1 mole of parent amide) the corresponding amounts were 32 %, 38.5 %, and 16 %, respectively. We have not studied these side-reactions in detail but we mention them here since they form an important limitation in the use of the second alkylation.

Presumably an exchange of a carbon atom adjacent to the α-carbon atom with an atom more electronegative than carbon ought to increase the activity of the α-hydrogen atom. We have therefore investigated two cases, R = phenoxy and R = diethylamino (both with Ar = phenyl and Y = diethylamino). These amides react easily with sodamide. The activity of their α-hydrogen atoms seems to be comparable with that of the amides of diphenylacetic acid or phenyl-2-pyridylacetic acid. The description of the alkylation of these two amides having phenoxy or diethylamino groups in α-position together with other data is given under Experimental.

EXPERIMENTAL

Most of the parent amides used have been prepared by the first alkylation procedure described by us earlier. The di*iso*propylamide of α-ethylphenylacetic acid (b.p. 112—116°/0.9 mm; m.p. 70—72°) and the diethylamide of α-allylphenylacetic acid (b.p. 120—122°/0.1—0.2 mm) have been prepared from the commercially available acids by conventional route *via* their acid chlorides.

α-Diethylamino-phenylacetic acid diethylamide has been obtained in good yield directly from the α-bromoacid chloride and diethylamine in benzene. B.p. 112—113°/0.1 mm.

α-Phenoxy-phenylacetic acid diethylamide has been prepared in good yield from the α-bromoacid chloride, which first has been converted to the diethylamide. This and sodium phenolate gave the desired α-phenoxy compound. In both cases benzene has been used as solvent. M.p. 101—102° (from benzene and petroleum ether). (Found: C 76.43; H 7.53; N 5.05. Calc. for $C_{18}H_{21}NO_2$ (283.4): C 76.29; H 7.47; N 4.94.)

α-Benzyl-α-(2-dimethylaminoethyl)-phenylacetic acid N,N-dimethylamide. Method I (with sodamide). 151.8 g (0.6 mole) of α-benzylphenylacetic acid N,N-dimethylamide, 24.2 g of commercial, ground sodamide and 600 ml of dry toluene are refluxed while stirring for about 2 h. After that time, the strong evolution of ammonia has decreased and a yellow precipitate of the sodium compound has been formed. The mixture is cooled to about 60°, a dried solution of 2-dimethylaminoethyl chloride (0.65 mole) in 200 ml of toluene is added and the mixture is warmed gently to reflux. Ammonia is evolved and the precipitate disappears. The reflux is continued for about 3 h. The reaction mixture is cooled to room temperature and then water is added carefully. The toluene layer is washed with water and extracted with dilute hydrochloric acid. The basic parts are precipitated by alkalisation of the united acid extracts and taken up in benzene. The benzene solution is dried, the benzene if driven off and the remaining oil is distilled. After a small fore-run, the desired α-(2-dimethylaminoethyl) compound distils at 160°/0.1 mm within an interval of a few degrees. It forms a viscous, faintly yellowish oil which crystallizes on standing. Yield 63 g (32.5 %). Recrystallization from petroleum ether gives 48.5 g (25 %) with m.p. 91—92°. For analyses, see Table 2. The remainder in the distilling flask is unimportant and scarcely more than the hold up volume.

By working up the toluene solution, a fraction, boiling at about 105°/1—2 mm, is received. It solidifies and gives after recrystallization from petroleum ether 40 g of 1,2-diphenylethane with m.p. 48—50°. (Found: C 92.06; H 7.93. Calc. C 92.26; H 7.74) It corresponds to 36.5 % of the parent amide.

22 g (14.5 %) of the parent amide could be isolated from a higher boiling fraction.

Method II (with phenylsodium). A solution of 38.0 g (0.15 mole) of α-benzylphenylacetic acid N,N-dimethylamide in 100 ml of dry toluene is dropped rapidly, while stirring, into a mixture of phenylsodium in toluene containing a slight excess of phenylsodium. The temperature of the contents increases from room temperature to about 50°. The mixture is now warmed to about 80°, and a dried solution of 2-dimethylaminoethyl chloride (from 27 g of the hydrochloride) in toluene is added while stirring during the course of about 15 min. The temperature rises somewhat (to about 95°), the brownish, precipitated salt is consumed but the colour remains almost unchanged. The mixture is now heated to 105—110° for about 1 h. The contents of the flask are cooled to room temperature, water is added carefully, and the toluene layer is washed with water. It is poured, while stirring, into dilute hydrochloric acid. The precipitated hydrochloride is taken on a filter, and washed with a small amount of cold water and ether. The yield of hydrochloride is 17.5 g (32 %). The base is liberated in a yield of 91.5 % from a warm water solution of the hydrochloride by means of dilute ammonia. M.p. 89—92°.

From the extracted toluene solution 10.5 g of 1,2-diphenylethane is obtained by distillation (b.p. 80—85°/0.2 mm), corresponding to 38.5 % of the parent amide. Another fraction (b.p. 140—145°/0.2 mm) consists of 6.0 g (16 %) of the parent amide.

α-(2-Dimethylaminoethyl)-α-(2′-pyridyl)-phenylacetic acid pyrrolidide.

Method I. A mixture of 53.3 g (0.2 mole) of α-(2-pyridyl)-phenylacetic acid pyrrolidide, 8.2 g of commercial, ground sodamide and 200 ml of dry toluene is refluxed for about 1 h or until the strong evolution of ammonia has decreased and a yellowish precipitate has been formed in the flask. The contents are cooled to about 50° and a dried solution of 2-dimethylaminoethyl chloride (from 33 g of the hydrochloride) in about 100 ml of toluene is added. The mixture is heated to reflux. After about 1 h reflux, the precipitate has disappeared and the second strong evolution of ammonia has decreased. After a total reflux of about 3 h, the contents are cooled to room temperature, water is added and the toluene layer washed with water. The toluene is driven off from the dried solution and the remaining oil is distilled. After a very small fore-run the main part distils at 192—195°/0.1 mm. This fraction, a reddish viscous oil, crystallizes on scratching with petroleum ether. Since it is soluble in this solvent cooling with dry ice decreases the losses. Yield 49 g (72 %). M.p. about 87°. Recrystallization from *cyclo*hexane raises the m.p. to 90—93°. After another two recrystallizations from acetone the m.p. is 93.5—95°, but the total yield has now decreased to 40 %. For analytical data see Table 1.

α-Benzyl-α-(2-morpholinoethyl)-phenylacetic acid N-benzyl-N-propyl-amide. (With KNH_2*).* A solution of 53.6 g (0.15 mole) of α-benzyl-phenylacetic acid N-benzyl-N-propyl-amide in 100 ml of dry toluene is added while stirring to a suspension of potassium amide in liquid ammonia (prepared from 5.9 g of potassium, about 200 ml of liquid ammonia and traces of ferric nitrate by conventional procedure). The cooling bath (dry ice and alcohol) is removed and the ammonia is allowed to evaporate through the reflux condensor. This process is facilitated by gently warming the flask by means of a heating lamp until the contents have reached room temperature. The colour of the contents is now brownish black. A solution of 22.5 g of recently distilled 2-morpholinoethyl chloride in 50 ml of dry toluene is added directly by means of a dropping funnel. The flask contents are heated to boiling and the reflux is continued for 2 h. Strong evolution of ammonia takes place during the first part of the heating, the colour of the mixture becomes paler and is yellowish white after 2 h. The mixture is cooled to room temperature, water is added and the toluene layer is washed with water. The basic components are extracted with dilute hydrochloric acid and the united acid solutions are treated with dilute sodium hydroxide. The precipitated oil is taken up in ether. When the ether is removed, the remaining oil solidifies, giving 33.5 g (47.5 %) of crystalline crude product with m.p. 122—136°. Recrystallization from *cyclo*hexane yields 16.5 g (24 %) of the α-morpholinoethyl compound. M.p. 137.5—139°. For analytical data see Table 2.

*α-*n*-Octyl-α-diethylamino-phenylacetic acid N,N-diethylamide.* A mixture of 26.2 g (0.1 mole) of α-diethylamino-phenylacetic acid N,N-diethylamide, 4.2 g of sodamide and 125 ml of dry toluene is refluxed for 1—2 h while stirring. The strong evolution of ammonia has then ceased but no precipitate has been formed in the brown-coloured contents of the flask. 20.0 g (theoret. 19.3 g) of *n*-octyl bromide is now slowly added (to the refluxing flask contents) by means of a dropping funnel and the reflux is continued for 6 h. After cooling to room temperature, water is added and the toluene layer is washed with water. The separated toluene layer is dried with anhydrous sodium sulphate, the toluene is driven off and the remaining oil is distilled in vacuo. After a fore-run of 4.0 g, consisting mainly of unreacted bromide and parent amide, a main fraction is collected at 165—168°/0.2 mm (28.7 g or 77 %) as an almost colourless, viscous oil. (Found: C 76.98; H 11.15; N 7.60. Calc. for $C_{24}H_{42}N_2O$ (374.6); C 76.95; H 11.30; N 7.48).

α-Benzyl-α-diethylamino-phenylacetic acid N,N-diethylamide. The alkylation was carried out in the same manner as in the preparation of the *n*-octyl compound described above. The benzyl compound distils as a viscous, faintly yellowish oil at 172—175°/0.1—0.2 mm. Yield 50 %. Recrystallizations from small amounts of petroleum ether give white crystals with m.p. 109.5—110.5°. (Found: C 78.47; H 9.24; N 8.00. Calc. for $C_{23}H_{32}N_2O$ (352.6): C 78.34; H 9.17; N 7.95).

*α-*n*-Octyl-α-phenoxy-phenylacetic acid N,N-diethylamide.* A mixture of 28.4 g (0.1 mole) of α-phenoxy-phenylacetic acid N,N-diethylamide, 4.2 g of sodamide and 125 ml of dry toluene is refluxed while stirring. After about 1 h reflux, the strong evolution of ammonia has ceased and the flask is filled with a grayish green precipitate. 20.0 g (theoret. 19.3 g) of *n*-octyl bromide is added to the refluxing mixture by means of a dropping funnel during the course of 15—30 min and the precipitate disappears. The reflux is continued for about 8 h. The reaction mixture is worked up in the usual manner. After a fore-run of 6.6 g, mainly consisting of unreacted parent amide, the α-*n*-octyl compound distils at 165—170°/0.1 mm as a viscous, faintly yellowish oil. Yield 26.0 g or 66 %. Redistillation gives 20.1 g (51 %). (Found: C 78.58; H 9.36; N 3.65. Calc. for $C_{26}H_{37}NO_2$ (395.6): C 78.93; H 9.43; N 3.54).

*α-*Neo*hexyl-α-phenoxy-phenylacetic acid N,N-diethylamide.* This compound is prepared analogously with the preceding one, but 17.0 g (theoret. 16.5 g) of *neo*hexyl bromide is used instead of octyl bromide. After a fore-run of 2.0 g, a main fraction (25.0 g or 68 %) distils at 150—152°/0.05—0.1 mm. In spite of the narrow interval, this fraction contains amounts of the parent amide of which about 5 g could be recovered by scratching the oil with petroleum ether. The mother liquor gave by cooling in a dry ice-alcohol bath 6.0 g of a compound with m.p. 71—73°. (Found: C 78.39; H 8.94; N 3.83. Calc. for $C_{24}H_{33}NO_2$ (367.5): C 78.43; H 9.05; N 3.81).

*a-(*p*-Chlorobenzyl)-a-phenoxy-phenylacetic acid N,N-diethylamide* is synthetized in the same way as the *n*-octyl derivative from 14.2 g (0.05 mole) of *a*-phenoxy-phenylacetic acid diethylamide. The *p*-chlorobenzyl chloride, dissolved in 25 ml of dry toluene, is added at a temperature of about 80°, followed by reflux for 3.5 h. A fore-run (up to 180°/0.1 mm) gives 5.0 g. The main fraction, 180—205°/0.1—0.2 mm (11.2 g or 55 %), gives, on recrystallization from small amounts of petroleum ether, 7.0 g (35 %) of *p*-chlorobenzyl compound, m.p. 101—102°. From the fore-run 0.8 g of parent amide and 1.0 g of *p*-chlorobenzyl derivative are isolated. (Found: C 73.70; H 6.46; N 3.43. Calc. for $C_{25}H_{26}ClNO_2$ (407.9): C 73.60; H 6.43; N 3.43).

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Errata: In the tables in our preceding papers (this journal **14** (1960) 1129 and 1151) in this series treating the "first alkylation" of carbonamides and the alkylation of sulphonamides, the following misprints occur:

p. 1137,	column	Formula, line 3: for $C_{16}H_{25}NO$	read	$C_{16}H_{25}NO_2$
pp. 1138—39,	»	Y: for $-[CH(CH_3)_2]_2$	»	$-N[CH(CH_3)_2]_2$
p. 1139,	»	R: for $-CH_2CH_2N_2(C_2H_5)$	»	$-CH_2CH_2N(C_2H_5)_2$
p. 1140,	»	R: for $-CH_2CH_2CH_2N[CH(CH_2)_3]_2$	»	$-CH_2CH_2CH_2N[CH(CH_3)_2]_2$
p. 1158,	»	R: (line 1): for phenyl	»	H

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