On the Alkylation Type Substitution and Ester Condensation at the α -Position of N,N-disubstituted Amides of Arylacetic Acids

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A simple method for substitution of alkylation type at the α -carbon atom of N,N-disubstituted arylacetic acid amides is described and discussed. Sodamide has been used as basic agent and toluene or benzene as reaction medium. Many compounds have been prepared according to the method and the result can be surveyed in tabular form. The aryl groups used in the investigation are phenyl, 1-naphthyl and 3-phenanthryl. No remarkable changes in reactivity as to sodium salt formation could be observed by these alternations of the aryl group, nor do variations in the substituents on the amide nitrogen change the activation of the α -hydrogen appreciably. The groups introduced are mainly of alkyl type but some heteroaromatic halogenides react in the same way. Condensations of esters (Claisen condensations) with the N,N-disubstituted amides have also been carried out with sodium methoxide or sodium ethoxide as condensing agents in the presence of an inert solvent (toluene or xylene), but this method seems to be less general than the substitution procedure, and somewhat unpredictable as to the results. However, cases including condensation under ring closure seem to form a subgroup in which the method is general.

In contrast to ester and nitrile groups, the activation by an amide group of the hydrogen at the adjacent carbon atom (the α -hydrogen) has been given comparatively little attention. The alkylation of esters and nitriles and ester (Claisen) condensation belong to the basic synthetic methods and have recently been reviewed ^{1,2}. As to the amides, unless the amide group is disubstituted, reactions generally occur under replacement of amide hydrogen. The main interest has therefore been connected to such reactions and not so much to the secondary effects caused by the amide group as a whole on the adjacent atoms and α -hydrogen in particular. (Since the reactions in the α -position can be studied mainly on N,N-disubstituted amides, for brevity, we omit this epithet unless otherwise stated.) It is also well known that an aryl group (*e.g.* phenyl) definitely activates the hydrogen at an adjacent carbon atom, an effect which

Fig. 1. Infrared spectrum of the parent amide 1-naphthylacetic acid N,N-diethylamide (a) and of its α -(2'-dimethylaminoethyl) derivative (b), showing that the frequency and intensity of the C=O bond of the amide group remain almost unchanged after substitu-

may be exemplified by the increasing mobility of α -hydrogen in the series toluene, diphenylmethane and triphenylmethane. The combined activation of α -hydrogen by an aryl group and nitrile and/or ester groups occurs in well known compounds such as phenylacetonitrile, phenylmalonic esters and phenylcyanoacetic esters. As to arylacetic acid amides, the mobility of the α -hydrogen of the amides of phenylacetic acid was expected to be between that of phenylacetonitrile and that of alkyl phenylacetate. The former compound easily forms a salt with sodamide in toluene in contrast to ethyl phenylacetate, which cannot be alkylated in the presence of sodamide in boiling toluene. It should be pointed out that the ability of salt formation and of alkylation depends very much on the basic agent used and the reaction conditions. The situation is quite different when such a strong agent as phenylsodium is used or when the salt formation is carried out with liquid ammonia as solvent. Thus, ethyl phenylacetate has recently been phenylated, too, in a yield of 63 % by bromobenzene in liquid ammonia and excess of sodamide³. In this paper we therefore intend merely to collect our experience and the results of a fairly extensive investigation in this laboratory^{4,5} of introducing groups in the α -position of arylacetic acid amides. For completeness some

tion. The frequency of ten another compounds investigated proved to be within the range 1 633–1 648 cm^{-1} . — All spectra are drawn with KBr pellet technique on a Unicam SP 100 IR instrument. The experimental error is $\pm 2 \text{ cm}^{-1}$.

comments have also been given to a patent by Cusic⁶ which turned up some years ago. He reports ten basically substituted cyclic amides of phenylacetic acids (they are included in Table 1). With the exception of one case in which sodamide has been used, lithium amide has been preferred as basic agent. The conventional method applied by us consists in substituting the amides in the presence of sodamide in an inert solvent, generally toluene. The reaction, which will be commented on below as to some practical details, can be written:

Ar = phenyl, substit. phenyl, 1-naphthyl or 3-phenanthryl,

Y = secondary amido group of various types

R = alkyl (mainly tertiary aminoalkyl), cycloalkyl, aralkyl and heteroaromatic radicals,

X = halogen

It is obvious that the reaction leads to substitution at the α -carbon atom and not to O-substitution. Thus the reaction product expected to be 2-phenyl-

(1,4)-butanedioic acid 1-(N,N-diethylamide)-4-(N-methylanilide) is converted by acid hydrolysis to phenylsuccinic acid in a yield of 90 %. Reduction of the amides with lithium aluminium hydride gives tertiary amines in very good yields (Table 2). Moreover, infrared spectra indicate that the carbonyl frequency remains almost unaltered after introduction of R (Fig. 1).

In the case of diphenylacetic acid amides the activation of the α -hydrogen is increased more by the second phenyl group and they form sodium salts more easily than when only one phenyl group is present. Indeed, substitution at the α -carbon atom by conventional methods has been applied ^{7,9} or probably applied ¹⁰ for synthetic purposes several times during the last years. In connection with the diphenylacetic acid amides it may also be pointed out that xanthene-9-carboxylic acid amides can be substituted at the 9-position by almost the same procedure (LiNH_2 or NaH in boiling toluene) as Cusic ¹¹ has shown. However, this is easily expected since the corresponding esters can already be substituted at this position under fairly simple conditions: the salt has been formed by boiling the ester solution in toluene with potassium ¹². Further, it may be noted that phenyl-2-pyridyl-acetic acid amides have been alkylated by the conventional method in this laboratory ⁴.

In addition to this substitution method, which may be interpreted as an alkylation in *sensu lato*, we have also tried to carry out ester (Claisen) condensations with some of the parent acid amides. This reaction which leads to β -ketoamides under liberation of alcohol from the ester with which the amide is condensed, seems to be much more limited as to its application. We now intend to treat these two cases separately in somewhat greater detail.

A. SUBSTITUTION OF ALKYLATION TYPE

According to our standard method for substitution (several examples are given in the experimental part) the amide is dissolved in benzene or toluene (generally 0.1 mole amide per 100 ml solvent), a slight excess of the theoretical amount of sodamide (commercial ground quality has been used) is added, and the mixture warmed to reflux under stirring. A strong evolution of ammonia generally begins before the mixture boils — at least when toluene is used as solvent. After refluxing during 1–2 h the strong evolution of ammonia ceases. (The strength of the ammonia evolution is easily followed by putting dry strips of indicator paper at the mouth of the reflux condensor.) At this time the sodium salt of the amide has formed a precipitate in the flask in most cases. The mixture is then cooled somewhat before the compound RX is added — the extent of cooling, of course, and the rate of adding the alkylating compound must be adapted to the reactivity of the latter. When the agent is added, the salt of the amide generally disappears, the temperature increases, and a second strong evolution of ammonia starts. This second "ammonia peak" probably originates from sodamide which has been enclosed in the sodium salt formed and now can react. When the salt of the amide (e.g. N-benzyl-N-propylamide of phenylacetic acid) is soluble the salt formation is more complete and the second "ammonia peak" less pronounced. The reaction is never violent. After the second ammonia evolution has decreased further boiling for 1–2 h is

generally enough to ensure a complete or almost complete reaction. Of course, to be certain, one ought to prolongate the reaction time when, for example, chlorides are used, as they are known to react slowly. In this case the sodium salt formed disappears slowly and the second "ammonia peak" is not pronounced.

As to the salt formation in toluene or benzene, in no case has this proved to occur at room temperature. Warming to above 50°C is necessary. Heating up to the boiling point of the reaction mixture is to be preferred in most cases. Thus phenylacetonitrile is much more reactive under the same conditions. On the whole the power of forming salts under our conditions varies very little with the substituents at the amide nitrogen. Heavy groups seem merely to increase the solubility of the sodium salt.

On the whole it is of fairly little importance how the substitution reaction is carried out. The procedure described above is of particular interest when the alkylating agent may react with the sodamide itself and one can hardly demand a higher yield than that corresponding to the sodium salt formed during the first reflux. Otherwise, at least on a small laboratory scale, one only has to mix the reacting compounds and the solvent and boil the mixture. Alternatively, one may add the sodamide in portions to the boiling mixture. Since the reaction time is fairly short, a loose cotton plug at the top of the reflux condenser is sufficient for exclusion of moisture. It may be removed during the periods of strong evolution of ammonia. The conditions are not rigorous. However, as in all cases when sodamide is used, its quality is very important for the success of the reaction. Too large an excess of sodamide should be avoided, since some of the alkylation products may be unstable under prolonged reflux with sodamide as has been proved by our attempts to carry out a second alkylation of these monoalkylated compounds.

We have chosen the easily available sodamide as basic agent with benzene or toluene as reaction media. In all the listed examples except one, Cusic⁶ has used lithium amide. Since no yields are given, it is difficult to say whether it is to be preferred to the less expensive sodamide. However, the yields obtained by using sodamide are generally so good, that there seems to be no reason to use other alkali amides.

Sodium hydride reacts very slowly in forming salts in benzene or toluene and we have not been able to use it with success. Phenylsodium in toluene has also been used as an agent in forming salts, but it is generally not necessary to use such a reactive compound. As far as we have tried it, it gives no advantages.

A single trial with phenylacetic acid pyrrolidide and di-*isobutyl*acetal suggests that the alkylation method of esters and nitriles by Weizmann *et al.*¹³ which uses potassium hydroxide in solvents of acetal type, is not applicable with success to our amides.

Other polar solvents such as diglyme (ethylene glycol dimethyl ether) and dioxane have also been tried. With sodium hydride and diglyme the reaction is very slow and the yield almost none. Dioxane and sodium hydride give somewhat better yields. When sodamide has been tried in combination with these solvents, we have not been able to isolate any substitution product from the reaction mixture. On the whole these attempts to replace toluene and

benzene with other "polar" solvents and/or to replace the sodamide with sodium hydride have not been encouraging enough to justify further work in order to improve these modifications.

The compounds RX used for the introduction of R are halogenides. Chlorides and bromides have mainly been used. Alkyl *p*-toluenesulfonates have been tried in a few cases without appreciable success. They seem to react too easily with the sodamide to be recommended. Epoxides (ethylene oxide has been used in a very few trials) do not seem to give unique reaction products. There are reasons to believe that some polymerisation occurs on the hydroxyl groups formed. When R contains one or more ester groups one must expect low yields, since competition reactions occur. However, R containing a N,N -disubstituted amide group (*e.g.* RX = chloroacetyl- N -methylaniline) behave better in this respect. Of course, R is not allowed to bear groups containing a hydrogen atom more active than that in the α -position of the amide, nor groups which may rearrange so that such structures are formed.

As mentioned in the introduction the aryl groups used are phenyl, 1-naphthyl and 3-phenanthryl. No appreciable differences in reactivity as to salt formation have been observed in this series during the synthetic work. Only in the phenyl case syntheses have been carried out with substituents in the aryl group, and then only when the substituent is a halogen atom. Even in this case we have not been able to establish definite differences in reactivity between the *o*-, *m*- and *p*-compounds and the unsubstituted amides which are of interest for the application of the general method used by us. The case where the phenyl group bears one lower alkyl group has also been reported ^{4,6}. The method is limited as to the substituents of the aryl group and does not allow substituents which contain a hydrogen atom more mobile than that in α -position, such as hydroxy or acetamino groups, nor groups which can rearrange to give such a hydrogen.

A disadvantage of the method is that compounds with small substituents (R) often may be difficult to separate from the parent compound. If R bears a basic group, or is a heavy one, the separation from the parent amide is easy. On the other hand disubstitution seems to be of little importance. On the whole, side reactions are rare. The introduction of a second group in the α -position by this method is generally not so easy as that of the first one. Longer reaction time and sometimes also a stronger salt-forming agent than sodamide are necessary. In some cases proximity effects may also make the introduction of a second group difficult.

Most of the compounds with aryl equal to phenyl or substituted phenyl are viscous, colourless or faintly yellowish oils. When solid, their melting points are generally lower than that of the parent amides. They are very soluble in most organic solvents — often also in petroleum ether — and are difficult to recrystallize in good yields. The group consisting of the α -pyridyl derivatives is an exception to these characteristics.

As to the practical use of the compounds prepared according to this substitution method, those with a tertiary amino group (*e.g.* R = dialkylamino-alkyl) have pronounced and interesting pharmacological properties. Some of the α -substituted amides are also valuable as intermediates for further synthetic work. At least for some compounds a further substitution in the α -position

can be carried out. That this is the case for the phenyl-(2-pyridyl)-acetic acid amides has been shown in this laboratory. Moreover, as far as we have tried, the amide group has been easily reduced to a tertiary amino group by the conventional lithium aluminium hydride method¹⁴ in excellent yield. We have included some amines (see Table 2) prepared according to this method and which do not seem to have been reported previously. Since a necessary condition for success in using this method in the reduction of N,N-disubstituted amides seems to be that there remains at least one hydrogen atom at the α -carbon, and this condition is fulfilled within the series, the reduction method can be expected to be generally applicable.

Finally, it may be noted that we have tried to apply the method to some thiocarbonamides without success. Thus, gentle heating of a mixture of sodamide, phenylthioacetylmorpholine and 2-morpholinoethylchloride in toluene in addition to ammonia causes evolution of hydrogen sulphide. No compound corresponding to a substitution product could be isolated from the refluxed mixture. Some phenylthioacetylmorpholine could be recovered.

B. ESTER (CLAISEN) CONDENSATION

As mentioned above, in contrast to the substitution of alkylation type in the α -position, the condensation of amides with esters need more care, and special conditions in each case, to insure the success of our method (sodium methoxide or sodium ethoxide as condensing agent with an inert solvent, generally toluene or xylene, as reaction medium). Several cases which lead to ring closure, under formation of 1-substituted 3-phenylpyrrolidine-2,4-diones and 1-substituted 3-phenylpiperidine-2,4-diones, have been investigated and they give fairly good to excellent yields, indicating that the method can be expected to be general in these cases. The success is more unpredictable when the condensation does not involve ring closure. At least some of the condensation products (*e.g.* α -methoxalyl-phenylacetic acid dimethylamide) seem to be very sensitive to alkali, thereby undergoing acid cleavage since fairly large amounts of acid corresponding to the ester (from oxalic acid diesters we obtain the monoesters) used can be isolated from the reaction mixture. This sensitivity to alkali is also characteristic for the purified condensation product. The reaction product must therefore be poured into a mixture of ice and dilute acid when worked up. In some cases we have been able to distil off only half the stoichiometric amount of alcohol. From these reaction mixtures we have not yet been able to isolate any condensation product but only the acid and the parent amide. The temperature sensitivity is also pronounced. When too high temperature is used during the reaction — for example when the alcohol formed is distilled off — no desired reaction product can be isolated, but a waxy or highly viscous, yellowish brown product remains after the solvent is removed. At this time we therefore report only those cases in which we have been successful.*

* Stronger condensing agents, such as phenylsodium have not yet been tried.

Table 1. Continued.

Aryl	Y	R	Yield	B.p. °C/mmHg M.p. °C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
phenyl	$-\text{N}(\text{C}_2\text{H}_5)_2$	$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ ⁱ	76	125 — 26/0.6	$\text{C}_{17}\text{H}_{27}\text{NO}$	78.11	10.41	5.36	77.61	10.35	5.42
»	»	$-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_3$	90	120 — 22/0.1	$\text{C}_{18}\text{H}_{28}\text{NO}$	78.49	10.61	5.09	78.00	10.45	5.24
»	»	$-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$ ⁱ	78	130 — 31/0.2	$\text{C}_{18}\text{H}_{28}\text{NO}$	72.96	9.57	5.32	72.89	9.48	5.28
»	»		68	135 — 45/0.3							
»	»	$-\text{CH}_2-\text{C}_6\text{H}_5$	52	87 — 88 ^b	$\text{C}_{18}\text{H}_{27}\text{NO}$	79.07	9.96	5.12	78.71	9.94	5.23
»	»	$-\text{CH}_2-\text{C}_6\text{H}_4\text{Cl}(p)$	72	135 — 38/0.2	$\text{C}_{19}\text{H}_{23}\text{NO}$	81.10	8.24	4.98	80.60	8.23	5.03
»	»	$-\text{CH}_2-\text{C}_6\text{H}_4\text{S}(p)$	60	62 — 63 ^b	$\text{C}_{19}\text{H}_{22}\text{Cl NO}$	72.25	7.02	4.43	72.75	7.09	4.45
»	»		71	136 — 40/0.1	$\text{C}_{17}\text{H}_{21}\text{NOS}$	71.04	7.36	4.86	70.86	7.40	5.20
»	»		53	200 — 03/0.2 glass	$\text{C}_{21}\text{H}_{25}\text{NO}_3$	74.31	7.42	4.13	73.75	7.56	4.28
»	»	$-\text{CH}_2\text{CH}_2\text{N} \begin{array}{c} \text{H} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array}$	60	143 — 45/0.1	$\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}$	75.45	10.00	9.26	75.21	9.92	9.02
»	»	$-\text{CH}_2\text{CH}_2\text{N} \begin{array}{c} \text{H} \quad \text{O} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array}$	68	167 — 68/0.3	$\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$	71.01	9.27	9.21	70.71	9.29	9.29
»	»	$-\text{CH}_2\text{CH}_2\text{N} \begin{array}{c} \text{H} \quad \text{O} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \end{array}$ $-\text{CH}_2\text{Br}$	89	~100 (hygrosc.)	$\text{C}_{19}\text{H}_{31}\text{BrN}_2\text{O}_2$			20.01 ^h			19.00 ^h
»	»	$-\text{CH}_2\text{CON}(\text{CH}_3)\text{C}_6\text{H}_5$	50	91 — 93 ^c	$\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_2$	74.52	7.74	8.28	74.38	7.70	8.27

Table 1. Continued.

Aryl	Y	R	Yield	B.p.°C/mmHg M.p.°C	Formula	Analyses %					
						Calc.		Found			
						C	H	N	C	H	N
phenyl	$-\text{N}(\text{C}_2\text{H}_5)_2$		52	95 — 96.5 c	$\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$	67.89	8.23	8.80	68.05	8.27	8.82
»	»	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	86	137 — 41/0.1	$\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}$	74.95	10.60	9.20	74.51	10.55	9.28
»	»	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	75	132.5 — 34.5 f	$\text{C}_{20}\text{H}_{35}\text{BrN}_2\text{O}$			20.01 ^h			19.4 ^h
»	»	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	77	185 — 90/1							
»	»		50	63 — 64.5 ab	$\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$	76.08	7.51	10.44	76.03	7.47	10.39
»	»		30	215 — 20/0.2							
»	»		23	105 — 107 c	$\text{C}_{19}\text{H}_{20}\text{NOS}$	70.34	6.21	8.64	70.37	6.31	8.65
»	$-\text{[CH(CH}_3)_2]_2$		57	128 — 32/0.2							
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	40	81 — 82.5 b and 88.5 — 89	$\text{C}_{20}\text{H}_{31}\text{NO}$	79.68	10.37	4.65	79.20	10.44	4.68
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	50	113 — 15/0.2							
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	46	35.5 — 37.5 b	$\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}$	74.43	10.41	9.65	74.36	10.51	9.43
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	81	115 — 16/0.1	$\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}$	75.42	10.76	8.80	74.59	10.64	8.78
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	90	143.5 — 44 c	$\text{C}_{20}\text{H}_{35}\text{ClN}_2\text{O}$			9.99 ^h			9.80 ^h
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	55	144 — 46.5 e	$\text{C}_{21}\text{H}_{37}\text{IN}_2\text{O}$						
»	»	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	78	130 — 35/0.2	$\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}$	75.85	10.91	8.43	75.34	10.95	8.56

able 1. Continued.

Aryl	Y	R	Yield	B.p.°C/mm Hg M.p.°C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
benzyl	$-\text{[CH(CH}_3)_2]_2$	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2\text{HCl}$ $-\text{CH(CH}_3\text{)-CO-N-}$	95	129 — 30 ^c	$\text{C}_{21}\text{H}_{37}\text{ClN}_2\text{O}$	69.96	8.95	9.88 ^h	70.03	9.07	9.51 ^h
»	»	»	20	100 — 05	$\text{C}_{21}\text{H}_{37}\text{N}_2\text{O}_3$	69.96	8.95	7.77	70.03	9.07	7.86
»	»	»	15	108 — 11 ^b	brown solid	76.99	8.16	9.45	77.09	8.15	9.47
»	»	»	55	deliq.	$\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$	76.25	11.06	22.0 ^b	76.40	11.19	20.0 ^b
»	»	»	45	104 — 106 ^{bc}	$\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$	76.25	11.06	8.09	76.00	11.01	8.30
»	»	»	50	deliq.	$\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$	76.25	11.06	8.09	76.00	11.01	8.30
»	$-\text{N(CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$	$-\text{CH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2$	83	135 — 37/0.1	$\text{C}_{22}\text{H}_{38}\text{N}_2\text{O}$	76.25	11.06	8.09	76.40	11.19	8.31
»	$-\text{N[CH}_2\text{CH(CH}_3)_2]_2$	$-\text{CH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2$	45	135 — 40/0.2	$\text{C}_{22}\text{H}_{38}\text{N}_2\text{O}$	76.25	11.06	8.09	76.00	11.01	8.30
»	$-\text{N-}$	$-\text{CH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2$	77	205 — 10/0.8	$\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}$	76.25	11.06	8.09	76.00	11.01	8.30
»	»	»	71	96 — 97 ^c	$\text{C}_{19}\text{H}_{29}\text{ClNO}$	72.71	6.42	4.46	72.47	6.46	4.45
»	»	»	81	152 — 57/0.4	$\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$	74.95	9.78	9.71	74.50	9.73	9.60
»	»	»	95	176 — 80/2 ^e	$\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$	74.95	9.78	9.71	74.50	9.73	9.60
»	»	»	95	177 — 79 ^c	$\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$	74.95	9.78	9.71	74.50	9.73	9.60
»	»	»	175 — 77 ^e	175 — 77 ^e	$\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$	74.95	9.78	9.71	74.50	9.73	9.60
»	»	»	55	108.5 — 110 ^{ab}	$\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}$	76.66	6.81	10.52	76.69	6.81	10.31
»	»	»	84	138 — 42/0.5	$\text{C}_{17}\text{H}_{26}\text{NO}$	78.71	9.72	5.40	78.23	9.51	5.39
»	»	»	65	100 — 102 ^{bc}	$\text{C}_{19}\text{H}_{28}\text{NO}$	79.39	10.17	4.87	79.12	10.15	4.82

Table 1. Continued.

Aryl	Y	R	Yield	B.p.°C/mmHg M.p.°C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
henyl			31	82 — 83 ^{bc}	$C_{20}H_{12}ClNO$	73.27	6.77	4.27	73.25	6.48	4.31
»	»	$-CH_2CH_2N(C_2H_5)_2$		177 — 79/2 ^e							
»	»	—, HCl		174 — 75 ^e							
»	»	$-CH_2CH_2N[CH(CH_3)_2]_2$		213 — 18/2 ^e							
»	»	—, HCl		188 — 90 ^e							
»	»	$-CH_2CH_2N$		216 — 19/2 ^e							
»	»	$-CH_2CH_2CH_2N(CH_3)_2$	46	160 — 64/0.4	$C_{18}H_{28}N_2O$	74.95	9.79	9.71	75.00	9.60	9.74
»	»	$-CH_2CH_2CH_2N(C_2H_5)_2$	55	159 — 66/0.2	$C_{20}H_{32}N_2O$	75.90	10.19	8.85	75.95	10.14	8.96
»	»	—, CH_3Br	72	157 — 59 ^f	$C_{21}H_{35}BrN_2O$			19.4 ^h			19.3 ^h
»	»	$-CH_2CH_2CH_2N[CH(CH_3)_2]_2$	65	182 — 83/0.4	$C_{22}H_{34}N_2O$	76.69	10.53	8.13	76.50	10.40	8.08
»	»	$-CH_2CH_2CH_2N$	68	175 — 78/0.1	$C_{21}H_{32}N_2O$	76.78	9.82	8.53	76.71	9.57	8.59
»	»		71	195 — 97/0.4							
»	»	$-CH_2(CH_2)_5CH_3$ ^k	66	72.5 — 3.5 ^{bc}	$C_{18}H_{28}N_2O$	77.11	7.19	9.99	77.25	6.95	9.95
»		$-CH_2$	45	172 — 75/0.6	$C_{19}H_{29}NO_2$	75.20	9.64	4.62	75.20	9.65	4.69
»	»		63	171 — 73/0.1							
			50	80.5 — 82 ^{ab}	$C_{19}H_{21}NO_2$	77.26	7.17	4.74	77.20	7.20	5.05

able 1. Continued.

Aryl	Y	R	Yield	B.p. °C/mm Hg M.p. °C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
henyl			34	219 — 24/0.3	$C_{21}H_{23}NO_4$	71.37	6.56	3.96	71.51	6.73	4.10
»	»	$-CH_2CH_2N(C_2H_5)_2$	77	156 — 60/0.3 207 — 15/2 ^e 185 — 86 ^e	$C_{13}H_{18}N_2O_2$	71.01	8.95	9.27	71.11	8.96	9.00
»	»	— — —, HCl									
»	»	$-CH_2CH_2CH_2N(CH_3)_2$	52	187 — 90/1	$C_{17}H_{24}N_2O_2$	70.31	9.03	9.65	69.72	9.06	9.70
»	»	$-CH_2CH_2CH_2N(C_2H_5)_2$	69	156 — 58/0.1	$C_{19}H_{26}N_2O_2$	71.66	9.50	8.80	71.20	9.57	8.83
»	»	— — —, $ClCH_2$	58	189 — 91 ^g	$C_{28}H_{37}ClN_2O_2$			7.97 ^h			7.80 ^h
»	»	$-CH_2CH_2CH_2N$		"oil" ^e							
»	»		65	195 — 98/0.4							
»	»	$CH_2CH_2CH_2CH_3$	51	84 — 85.5 ^{ab}	$C_{17}H_{18}N_2O_2$	72.32	6.43	9.92	72.60	6.50	9.92
»			63	195 — 97/0.1	$C_{23}H_{32}ClNO$	75.44	8.11	3.52	75.73	8.18	3.66
»	»	$-CH_2CH_2CH_2N$	59	202 — 04/0.2	$C_{28}H_{42}N_3O$	78.34	10.62	7.03	78.50	10.60	7.14
;	$-N(cycloC_6H_{11})_2$	$-CH_3-C_6H_4Cl(p)$	50	225 — 30/0.2 glass-like	$C_{27}H_{34}ClNO$	76.48	8.08	3.30	76.39	8.12	3.39

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
benzyl	$-\text{N}(\text{cycloC}_6\text{H}_{11})_2$ $\text{CH}_3\text{CH}_2\text{CH}_3$	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$, HCl	37	204 — 07	$\text{C}_{28}\text{H}_{43}\text{ClN}_2\text{O}$	71.77	9.73	6.44	71.84	10.10	6.34
"	$-\text{N}-\text{CH}_2-\text{C}_6\text{H}_5$	$-\text{CH}_3-\text{C}_6\text{H}_5$	90	200 — 203/0.2	$\text{C}_{31}\text{H}_{37}\text{NO}$	83.99	7.61	3.92	83.98	7.62	3.94
"	"	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	64	168 — 72/0.4	$\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}$	78.06	8.93	8.28	77.65	8.88	8.20
"	"	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	51	175 — 80/0.2	$\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}$	78.64	9.35	7.64	78.33	9.35	7.50
"	"	$-\text{CH}_2-\text{HCl}$		123 — 24.5 °	$\text{C}_{24}\text{H}_{33}\text{ClN}_2\text{O}$			8.80 ^b			8.72 ^b
"	$-\text{N}(\text{CH}_3)-\text{C}_6\text{H}_5$	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	62	156 — 58/0.3	$\text{C}_{31}\text{H}_{43}\text{N}_2\text{O}$	77.73	8.70	8.63	77.54	8.66	8.39
"	"	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	77	170 — 74/0.3	$\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}$	78.06	8.93	8.28	77.70	8.97	8.13
"	"	$-\text{CH}_2-\text{CH}_2\text{Br}$	98	157 — 59	$\text{C}_{23}\text{H}_{33}\text{BrN}_2\text{O}$			18.44 ^h			18.30 ^h
"	"		50	89 — 93							
"	$-\text{N}(\text{C}_6\text{H}_5)_2$	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	41	97 — 98.5 °	$\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}$	79.44	6.00	9.27	79.14	6.03	9.18
"	"	$-\text{CH}_2-\text{CH}_2\text{Br}$	65	225 — 26/0.8	$\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}$	80.79	7.82	7.25	80.30	7.93	7.29
"	"	$-\text{CH}_2-\text{CH}_2\text{Br}$	82	191 — 93 °	$\text{C}_{27}\text{H}_{33}\text{BrN}_2\text{O}$			16.60 ^h			16.40 ^h
chloro-benzyl	$-\text{N}(\text{CH}_3)_2$	$-\text{CH}_2\text{CH}_2\text{N}(\text{H})$	85	145 — 50/0.2	$\text{C}_{17}\text{H}_{25}\text{ClN}_2\text{O}$	66.11	8.16	9.07	65.85	8.07	9.01

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
<i>n</i> -chloro-phenyl	$-\text{N}(\text{CH}_3)_2$	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	54	152 — 54/0.2	$\text{C}_{17}\text{H}_{27}\text{ClN}_2\text{O}$	65.68	8.76	9.01	65.84	8.84	9.14
<i>p</i> -chloro-phenyl	$-\text{N}(\text{CH}_3)_2$	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$, HCl		113 — 16	$\text{C}_{17}\text{H}_{25}\text{Cl}_2\text{N}_2\text{O}$			10.18 ^h			10.2 ^h
		$-\text{---}, \text{CH}_3\text{Br}$	71	glass-like	$\text{C}_{18}\text{H}_{29}\text{BrClN}_2\text{O}$			19.7 ^h			18.6 ^h
<i>p</i> -chloro-phenyl	$-\text{N}(\text{CH}_3)_2$	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	86	165 — 70/0.3	$\text{C}_{17}\text{H}_{27}\text{ClN}_2\text{O}$	65.68	8.76	9.01	65.80	8.85	8.74
		90	180 — 205/0.2
		80	75 — 76.5 °C	$\text{C}_{18}\text{H}_{25}\text{ClN}_2\text{O}$	65.57	5.50	10.20	65.95	5.55	10.15
		$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	70	69.5 — 70 °C	$\text{C}_{17}\text{H}_{25}\text{ClN}_2\text{O}$	67.43	6.33	9.25	67.30	6.38	9.09
		70	154 — 56/0.15							
<i>p</i> -bromo-phenyl	$-\text{N}(\text{C}_2\text{H}_5)_2$		45	87.5 — 89 °C	$\text{C}_{17}\text{H}_{24}\text{ClNO}_2$	65.90	7.81	4.52	65.71	7.68	4.70
		190 — 200/1 ⁴
		210 — 20/1 ⁴							
<i>p</i> -tolyl		$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$		210 — 20/1 — 1.5 ⁶							
<i>p</i> -tolyl				180 — 85/1 ⁴							
<i>p</i> -iso-propyl-phenyl		$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{H})$		220 — 30/1 ⁶							

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
naphthyl	$-\text{N}(\text{C}_4\text{H}_9)_2$	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	76	66 — 67 b	$\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}$	76.88	9.04	8.97	76.70	9.03	9.15
•	•	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$		186 — 87	$\text{C}_{21}\text{H}_{31}\text{BrN}_2\text{O}$			19.64 ^h			19.2 ^h
•	•	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	59	165.5 — 66 ab	$\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}$	79.21	6.97	8.80	79.30	6.95	8.74
•	$-\text{N}[\text{CH}(\text{CH}_3)_2]_2$	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_6\text{H}_5)_2$	71	175 — 78/0.15	$\text{C}_{23}\text{H}_{29}\text{NO}$	83.52	8.13	3.90	83.25	8.29	4.25
•	•	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	77	180 — 82/0.4							
•	•	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_4\text{H}_9)_2$	50	69.5 — 70 b	$\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}$	78.21	9.85	7.60	78.25	9.85	7.74
•	•	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_4\text{H}_9)_2$	69	185 — 87/0.2	$\text{C}_{23}\text{H}_{36}\text{N}_2\text{O}$	78.48	10.01	7.32	78.11	9.96	7.34
•	•	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	50	143 — 47 a							
phenan- ryl	$-\text{N}(\text{C}_4\text{H}_9)_2$	$-\text{CH}_2\text{CH}_2\text{N}(\text{C}_6\text{H}_5)_2$	67	123 — 24 d	$\text{C}_{27}\text{H}_{27}\text{NO}$	85.00	7.13	3.67	84.52	7.15	3.77
•	•	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	58	58 — 60 b	$\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}$	79.51	8.34	7.73	79.64	8.29	8.07

Table 2. Tertiary amines prepared from α -substituted N,N-disubstituted arylacetic acid amides by reduction with LiAlH₄.

$$\text{Aryl}-\text{CH}-\text{CH}_2-\text{Y} \quad \text{R}$$

Aryl	Y	R	Yield	B.p. °C/mm Hg M.p. °C	Formula	Analyses %					
						Calc.			Found		
						C	H	N	C	H	N
phenyl	$-\text{N}(\text{C}_2\text{H}_5)_2$	$-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2$	92	142–44/8	$\text{C}_{18}\text{H}_{31}\text{N}$	72.57	10.83	4.70	72.88	11.12	4.74
	$\rightarrow$ —, HCl	$\rightarrow$ —	83	162–63 (methanol + petr. ether)	$\text{C}_{18}\text{H}_{32}\text{ClN}$	79.10	11.18	9.71	78.80	11.22	9.84
•	$-\text{N}(\text{C}_2\text{H}_5)_2$		84	120–24/0.5	$\text{C}_{19}\text{H}_{32}\text{N}_2$	74.95	10.60	9.20	74.93	10.69	9.06
	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	82	150–58/1	$\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}$	80.48	10.13	9.39	80.28	9.66	9.16
1-naphthyl	$-\text{N}(\text{C}_2\text{H}_5)_2$	$-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	88	140–42/0.4	$\text{C}_{20}\text{H}_{30}\text{N}_2$						

EXPERIMENTAL

The amides used as starting materials have generally been prepared from the appropriate secondary amines and acid chlorides with benzene as solvent. In fairly few cases the Schotten-Baumann reaction has been applied. The yields are generally excellent or at least good. Several of these amides have been prepared earlier but some do not seem to have been reported previously. Since we find it practical, we have collected the boiling points and/or melting points of all amides used by us (however, the boiling points of the amide esters used in cyclic condensation have been listed in Table 3):

Phenylacetic acid: dimethylamide, b. p. 125–29°/0.7 mm, m. p. 40°; diethylamide, b. p. 111–13°/0.3 mm; diisopropylamide, m. p. 50–53°; di-*n*-butylamide, b. p. 122–24°/0.1 mm; diisobutylamide, b. p. 113–16°/0.1 mm; dicyclohexylamide, m. p. 83–85°; cyclohexyl-*n*-butylamide, b. p. 148–50°/0.2 mm; benzyl-*n*-propylamide, b. p. 176–78°/0.8 mm; dibenzylamide, m. p. 60.5–62.5°; diphenylamide, m. p. 74–75°; pyrrolidide, m. p. 47–48.5°; piperidide, b. p. 174–79°/8 mm; morpholide, m. p. 65.5–67°.

o-Chlorophenylacetic acid: dimethylamide, m. p. 54–54.5°.

m-Chlorophenylacetic acid: dimethylamide, b. p. 124–25°/0.2 mm.

p-Chlorophenylacetic acid: dimethylamide, b. p. 144–45°/0.4 mm; diethylamide, b. p. 120–25°/0.2 mm; morpholide, m. p. 103–05°.

α -Naphthylacetic acid: diethylamide, m. p. 77.5–79°; diisopropylamide, m. p. 84–85°.

Phenanthrene-3-acetic acid: diethylamide, m. p. 94–95°.

A. Examples of substitution of alkylation type

α -(*p*-Chlorobenzyl)-phenylacetic acid pyrrolidide. In a three-necked 500 ml flask, equipped with a reflux condensor, a mechanical stirrer and a dropping funnel, a mixture of 37.9 g (0.2 mole) phenylacetic acid pyrrolidide (m. p. 47–48.5°), 8.2 g (0.21 mole) commercial, ground sodamide and 200 ml of dry toluene is warmed. At about 80° a strong evolution of ammonia begins. After boiling for about 2 h the strong evolution of ammonia has ceased, and a white precipitate of the sodium salt of the pyrrolidide has been formed. The mixture is now cooled to room temperature. A solution of 33.6 g (0.21 mole) *p*-chlorobenzylchloride in 50 ml of dry toluene is added during a period of about 15 min. by means of the dropping funnel. The temperature in the flask increases to about 60° and the salt disappears. The solution becomes rose-coloured but this colour soon becomes pale as the sodium chloride is formed. The flask is warmed again to reflux. At this point a further strong evolution of ammonia begins but decreases after a boiling time of about 30 min. After further reflux for 2 h the evolution of ammonia has ceased almost completely. The mixture is now cooled to room temperature and cold water added carefully. After one further washing with water the toluene layer is dried with fused magnesium sulphate. The toluene is distilled off under diminished pressure. The remaining oil is distilled and the fraction 205–210°/0.8 mm is collected. Yield 48 g (76.5 %). The oil crystallizes almost immediately, m. p. 92–95°. Recrystallization from 100 ml cyclohexane gives 43.5 g (70.5 %) of white crystals, m. p. 96–97°. For analysis see Table 4.

α -Cyclohexyl-phenylacetic acid diisopropylamide. 109.7 g (0.5 mole) of phenylacetic acid diisopropylamide are dissolved in 400 ml of dry toluene, 21 g of sodium amide are added and the mixture refluxed for about 2 h or until the rapid evolution of ammonia has decreased and a large precipitate is obtained in the flask. 65 g (theoret. 59.3 g) of cyclohexylchloride are added gradually to the boiling mixture. During this procedure the salt reacts and disappears and evolution of ammonia takes place. The refluxing is then continued for about 5 h. After cooling to room temperature and twice shaking the reaction mixture with water, the toluene layer is dried with anhydrous sodium sulphate and the solvent distilled off. The main part of the remaining oil distils at 128–132°C/0.1 mm Hg. It solidifies to a mass of crystals. Yield 85 g (57 %). 5.0 g recrystallized from petroleum ether gives 3.5 g (total yield 40 %) of α -cyclohexyl-phenylacetic acid diisopropylamide, m. p. 81–82.5° and 88.5–89°C. For analytical data see Table 1.

Table 3. Ester condensations.

Reactant(s)	Product	Yield %	M.p. °C (solvent)	Analyses					
				Calc.			Found		
				C	H	N	C	H	N
$C_6H_5CH_2CON(CH_3)_2$ + dimethyl oxalate	$C_6H_5CHCON(CH_3)_2$ COCOOCH ₃	62 52	92-96 (benzene + petroleum ether)	62.64	6.07	5.62	62.62	6.10	5.63
$C_6H_5CH_2CON(CH_3)_2$ + diethyl oxalate	$C_6H_5CHCON(CH_3)_2$ COCOOCH ₂ CH ₃	65	~ 100						
$C_6H_5CH_2CON(C_2H_5)_2$ + ethyl nicotinate	$C_6H_5CHCON(C_2H_5)_2$ CO-	45	98-100 (benzene + petroleum ether)	63.86	6.51	5.41	64.09	6.54	5.41
	80 68.5	129-133 (benzene + petroleum ether)	72.95	6.80	9.45	73.36	6.94	9.49
$C_6H_5CH_2CON(CH_3)_2$ + $C_2H_5OOC-CH_2-$ B.p. 198-202°/0.5 mm		theor. 58	210-212 (butanol)	76.95	5.70	5.28	76.66	5.70	5.24
$C_6H_5CH_2CON(CH_3)_2$ + $CH_3OOC-CH_2-$ B.p. 150-153°/0.2 mm		60	135-137 (acetone)	70.91	6.45	6.89	70.80	6.50	6.86
$C_6H_5CH_2CON(CH_3)_2$ + $CH_3OOC-CH_2-$ B.p. 154-156°/0.5 mm		81 67	124-127.5 128-130 (ether + petroleum ether)	72.30	7.41	6.06	72.66	7.45	6.10

^a This compound is listed by Petersen & Weidemann¹⁵ but no data and references at all are given.

Table 3. Continued.

Reactant(s)	Product	Yield %	M.p. °C (solvent)	Analyses					
				Calc.			Found		
				C	H	N	C	H	N
<div> </div> <div>B.p. 202–207°/0.7 mm</div>	<div> </div>	72	138.5–140 (ether + petroleum ether)	77.39	6.14	5.01	73.69	6.17	5.10
<div> </div> <div>B.p. 175–177°/0.3 mm</div>	<div> </div>	theor. 86	220–225° 222–226 (ethanol)	76.47	5.22	5.58	76.51	5.21	5.60

α -(2-Diethylaminoethyl)-phenylacetic acid diisopropylamide. 109.7 g (0.5 mole) of phenylacetic acid diisopropylamide, dissolved in 450 ml of dry toluene is boiled while stirring with 21 g of sodium amide for about 2 h. After that time the strong evolution of ammonia has ceased and a yellow precipitate has been formed in the flask. After cooling to about 50°C, a dried solution of 2-(diethylamino)-ethylchloride (liberated from 98 g of the hydrochloride) in ca. 200 ml of toluene is added. The reaction mixture is gently warmed until the reaction begins, *i. e.*, the sodium salt dissolves and evolution of ammonia increases. The reaction mixture is then refluxed for about 3 h. The mixture is cooled to room temperature and water is added carefully. The toluene layer is then washed two times with water and then extracted two times with dilute hydrochloric acid. The base is liberated from the acid solution with dilute sodium hydroxide. The precipitated oil is dissolved in ether and the water phase extracted once more with ether. The united ether solutions are dried with anhydrous sodium sulphate and the ether evaporated. The main part of the remaining oil distils at 115–20°C/0.1 mm and consists of the α -diethylamino-ethyl compound. Yield 128 g (81 %).

The hydrochloride precipitates as an oil when ethanolic hydrochloric acid is added to an ether solution of the base. When the acid containing ether is decanted and, to secure basic reactions ether with further base is added the hydrochloride solidifies, m.p. 142–4°C.

To 9.6 g (0.02 mole) of the α -(2-diethylaminoethyl)-phenylacetic acid diisopropylamide, dissolved in 100 ml of dry ether, is added 5.5 g of methyl iodide, dissolved in 50 ml of dry ether. After two days 8.4 g of methylammonium compound is filtered off. After recrystallization from a mixture of ethanol and ether 7.7 g (57 %) is collected, m. p. 144–5°C. For analytical data see Table 1.

α -(2-Dimethylaminoethyl)- α -(α' -naphthyl)-acetic acid diethylamide. To 48.3 g (0.2 mole) of α -naphthylacetic acid diethylamide dissolved in 200 ml of dry toluene are added 8.2 g of sodium amide and the mixture is boiled for about 2 h while stirring until the rapid evolution of ammonia has ceased and a yellowish precipitate has been formed. After cooling down to about 50°C, an amount of 2-(dimethylamino)-ethyl chloride, prepared from 35 g of the hydrochloride, dissolved in about 150 ml toluene is added. The mixture is slowly heated, whereby the precipitate is dissolved and ammonia is evolved. The mixture is then refluxed for about 4 h. After cooling, the mixture is shaken two times with water and then extracted two times with dilute hydrochloric acid. The base is liberated from the acid solution by means of dilute sodium hydroxide and dissolved in benzene. The benzene layer is separated and the water phase extracted one time with benzene. The benzene solutions are united and the benzene is driven off. A solidifying oil is obtained. After recrystallization from petroleum ether (cooling with dry ice and ethanol) the α -(2-dimethylaminoethyl) compound is obtained in a yield of 76 % (47 g), m. p. 62–63°C. For analytical data see Table 1.

α -(3-Diethylaminopropyl)-phenylacetic acid morpholide. A mixture of 82.1 g (0.4 mole) of phenylacetic acid morpholide, 350 ml of dry toluene and 16.4 g of sodium amide is refluxed for about 3 h until the strong evolution of ammonia has ceased. The mixture is cooled to about 70°C and 63 g (theoret. 60.0 g) of 3-(diethylamino)-propyl chloride is added gradually. Thereafter the mixture is warmed and refluxed for about 3 h. After cooling to room temperature the reaction mixture is worked up as described in the previous example. After a fore-run of about 20 g the substituted morpholide distils at 156–158°C/0.1 mm. Yield 88 g (69 %). The remainder in the distilling flask is insignificant. For analysis see Table 1.

B. Examples of ester (Claisen) condensation

α -Methoxalyl- and α -ethoxalyl-phenylacetic acid dimethylamide. Sodium ethoxide is prepared from 4.8 g (0.21 mole) of sodium and 15 ml of absolute ethanol in 100 ml of dry xylene and the excess of alcohol is distilled off. At room temperature a solution consisting of 32.6 g (0.2 mole) of phenylacetic acid dimethylamide, 30 g (29.2 g = 0.2 mole) of diethyl oxalate and 50 ml of xylene is added to this mixture. The reaction mixture is warmed gently to 85° and kept at this temperature for about 45 min. The reaction mixture is cooled to room temperature and put into a mixture of 75 ml 5 N HCl and ice. Crystals begin to separate from the xylene layer and further precipitate is formed when 200 ml

of petroleum ether is added. The crude product is filtered off, yielding 27 g of the ethoxalyl compound. From the mother liquor another 7.5 g can be obtained with approximately the same melting point, 97–100°. Total yield 65.5 %. Recrystallization from a mixture of benzene and petroleum ether gives 23.5 g (total yield 45 %) with melting point 98–100°. For analytical data see Table 3.

When dimethyl oxalate and sodium methoxide are used, almost the theoretical amount of methanol can be distilled off. The crude yield is 32 g (62 %). After two recrystallizations from a mixture of benzene and petroleum ether the yield is 20 g (40 %). See also Table 3.

α-Nicotinoyl-phenylacetic acid diethylamide. Sodium ethoxide is prepared from 4.8 g of sodium and 15 ml of absolute ethanol, in 100 ml of dry xylene and the excess of ethanol is distilled off. At room temperature a mixture of 38.2 g (0.2 mole) of N,N-diethylphenylacetamide, 30.2 g (0.2 mole) of ethylnicotinate and 100 ml dry xylene is added to the sodium ethoxide suspension during stirring. The mixture is now warmed gently, and in the course of about 2.5 h about the theoretical amount of ethanol (ca. 27 ml) is distilled off. The mixture is then cooled to room temperature and cold water is added. The sodium salt dissolves. The xylene phase is separated and the water phase washed with ether. To the water phase is now added 5 N hydrochloric acid until pH is about 4. The precipitate is collected on a funnel and washed with water. The dried, slightly yellow crude product (47.5 g, 80 %) melts at 129–133°. Recrystallization from a mixture of benzene (100 ml) and petroleum ether (100 ml) raises the m. p. to 136–138°. A further recrystallization from a mixture of benzene and cyclohexane gives 40.5 g (68.5 %), m. p. 136–138°. For analytical data see Table 3.

1-Methyl-3-phenyl-quinoline-2,4-(1H,3H)-dione. 28.2 g (0.1 mole) methyl N-methyl-N-phenacetylthranilate, dissolved in 50 ml dry toluene is added to sodium methoxide (from 2.7 g sodium) in ca. 50 ml dry toluene at room temperature while stirring. A precipitate is formed. The mixture is warmed and the theoretical amount of methyl alcohol is distilled off. After cooling to room temperature the precipitate is dissolved by adding cold water, and the separated water solution washed with ether. The solution is acidified with 5 N hydrochloric acid, and the precipitate filtered off and washed with water. Yield 24.8 g (99 %), m. p. 220–224°. Recrystallization from 700 ml of ethanol gives 21.5 g (86 %), m. p. 222–226°. For analytical data see Table 3.

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