hour the next, decomposing with 100 ml. of saturated ammonium chloride solution, and working up in the usual manner gave 10.7 g. (91%) of crude carbinol boiling at 76–84° (0.7 mm.). This thrice redistilled gave 6 g., b. p. 77–78° (0.3 mm.), $n^{20.6}D$ 1.5150.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 80.5; H, 11.2; hydrogenation, Adams catalyst, 1.1 double bonds.

Allophanate.—One gram of dimethylnaphthitenol and 120 ml. of a solution of 9 equivalents of cyanic acid in ether were mixed and let stand one day in refrigerator and one day at room temperature. Only a small amount of solid precipitated. Evaporation of the ether, extraction of the residue with benzene, evaporation of the benzene from the extract, and crystallization of the residue from methanol gave 0.5 g. of product, m. p. 171–172.6° (dec.). Additional crystalline material, 0.3 g., m. p. below 135°, which was not further investigated, was obtained from the residue from the methanol mother liquor with Skellysolve "B"–ether. Repeated recrystallization of the main fraction from methanol and finally from methanol containing 10% of benzene gave a dimethylnaphthitenyl allophanate, m. p. 178.8–179.6° (dec.).

Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.1; H, 8.3; N, 10.5. Found: C, 63.2; H, 8.5; N, 10.6.

1-Ethynyl-10-methyl-5,10-*cis*?-7?-naphthiten-1-ol.—A solution of sodium acetylide was prepared by saturating about 600 ml. of liquid ammonia with acetylene which had been passed through sulfuric acid and over potassium hydroxide, dissolving 5.7 g. of sodium in the liquid ammonia–acetylene, and then passing acetylene in for twenty minutes more. Sixteen grams of methylnaphthitenone in 50 ml. of ether was dropped into the sodium acetylide solution during forty-five minutes, the mixture was stirred for four hours, and let stand overnight with evaporation of the ammonia. Addition of ice, ether and benzene to the residue, acidification to litmus with acetic acid, separation of the ether–benzene solution, extraction of the aqueous part with ether, washing the combined extracts with sodium bicarbonate solution, then with saturated sodium chloride solution, drying over sodium sulfate, evaporation of solvents, and distillation gave 1.8 g. of unchanged methylnaphthitenone and 14.5 g. (90%) of crude carbinol, b. p. 85–94° (0.6 mm.), which twice redistilled gave ethynylmethylnaphthitenol, 12 g., b. p. 76–78° (0.3 mm.), $n^{19.6}D$ 1.5275.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.1; H, 9.5. Found: C, 82.1; H, 9.5.

This carbinol gives a pinkish-white precipitate with silver nitrate in ammonium hydroxide–methanol. No formation of water was seen when the carbinol was heated alone at 275° or with iodine at 200°. After heating under these conditions, all of the material distilled (b. p. about 193° (193 mm.) and b. p. 135–139° (13 mm.) respectively). The refractive index was not changed.

Summary

10-Methyl-*cis*?-7?-naphthiten-1-one has been prepared from butadiene and 1-methyl-1-cyclohexen-6-one. Two 1-alkyl-1-carbinols were prepared from the ketone.

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Acylations of Esters with Esters to Form β-Keto Esters Using Sodium Amide[1,2]

BY JOSEPH C. SHIVERS, MARCUS L. DILLON AND CHARLES R. HAUSER

The acylation of esters with esters to form β-keto esters has generally been effected by sodium alkoxides[3] or, when these reagents fail, by sodium[3] or potassium[4] triphenylmethide. Relatively few of these condensations have previously been effected by sodium or potassium amide. Sodium amide has been found more effective than sodium alkoxides for the analogous acylations[5] or carbethoxylations[6] of ketones, and, when it is applicable, sodium amide should also be more effective for the acylation of esters. Indeed, the amide ion should be even more effective than the triphenylmethide ion because it is a stronger base. However, the application of sodium amide to the acylation of esters is limited by the fact that the amide ion often converts the ester to the corresponding amide[7] instead of to the ester anion, which is the reactive intermediate in the condensation. Nevertheless, on the basis of a recent study[8] on the influence of structure of esters on the proportions of ester anion and amide formed, it has become possible to extend considerably the number of acylations of esters using sodium amide. Various self and mixed-ester condensations using this reagent are described in the present investigation.

Self-condensations.—Preliminary experiments with *n*-amyl acetate indicated that the condensations were best effected by adding the ester, in 10% excess, to sodium amide in liquid ammonia, replacing the ammonia by ether and refluxing the mixture, although other conditions also produced satisfactory yields in certain cases.

Sodium amide (0.3 mole) in 300 ml. of anhydrous ammonia was prepared as described previously[5,6] in a one-liter three-necked round-bottomed flask equipped with a mercury-sealed stirrer, dropping funnel and condenser having a tube of drierite. With the drying tube removed, 0.33 mole of the ester in an equal volume of dry ether was

(1) Paper XXXVII on "Condensations"; paper XXXVI, THIS JOURNAL, **68**, 2647 (1946).

(2) This investigation was supported in part by a grant from the Duke University Research Council.

(3) See Hauser and Hudson, "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, New York, N. Y., 1942, Vol. I, Chap. IX.

(4) Levine, Baumgarten and Hauser, THIS JOURNAL, **66**, 1230 (1944).

(5) Adams and Hauser, *ibid.*, **66**, 1220 (1944); Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945).

(6) Levine and Hauser, *ibid.*, **66**, 1768 (1944).

(7) For a discussion of four types of reactions that esters may exhibit with bases, see Hauser, Shivers and Skell, THIS JOURNAL, **67**, 409 (1945).

(8) Hauser, Levine and Kibler, *ibid.*, **68**, 26 (1946).

TABLE I[a]

SELF CONDENSATION OF ESTERS WITH SODIUM AMIDE

Ester	β-Keto ester	Yield, %	B. p., °C.	Mm.
Ethyl acetate	Ethyl acetoacetate	23[b]	109	80
n-Propyl acetate	*n*-Propyl acetoacetate	61	79–80[c]	11
i-Propyl acetate	*i*-Propyl acetoacetate	57	74–77[d]	15
n-Butyl acetate	*n*-Butyl acetoacetate	40	90–93[c,e]	11
n-Amyl acetate	*n*-Amyl acetoacetate	40	107–108[f]	15
2-Ethylbutyl acetate[g]	2-Ethylbutyl acetoacetate	49	142–143[h]	40
Benzyl acetate	Benzyl acetoacetate	52	162–164[i]	16
α-Phenylethyl acetate	α-Phenylethyl acetoacetate	58	149–152[j]	10
Ethyl phenylacetate	Ethyl α,γ-diphenylacetoacetate	82	77–78 (m. p.)[k]	
Ethyl propionate	Ethyl α-propionylpropionate	31	88–90[c,l]	12
n-Butyl propionate	*n*-Butyl α-propionylpropionate	5	111–112[l,m]	15
Ethyl *n*-butyrate	Ethyl α-butyrylbutyrate	31	102–105[c,n]	12
Ethyl *i*-valerate	Ethyl α-*i*-valeryl-*i*-valerate[o]	0	.....	..

[a] Boiling and melting points are uncorrected. Analyses are by Arlington Laboratories, Fairfax, Virginia. [b] Obtained by adding the ester to a stirred ether suspension of sodium amide; in working up the reaction mixture, the aqueous phase was saturated with sodium chloride before extraction with ether. Yields of only 5–10% have previously been obtained using sodium or potassium amide; see note (1) ref. (9). [c] Boiling point agrees essentially with that reported in the literature; see ref. 11. [d] Reported b. p. 75–76° at 15 mm. [Moureu and Delange, *Bull. soc. chim.*, [3] **27**, 378 (1902)]. [e] *n*-Butyl acetate (25%) was recovered. [f] Reported b. p. 105–108° at 15 mm. (see ref. in note *d*). Our product also distilled at 139–140° at 50 mm. *n*-Amyl acetate (13%) was recovered. [g] We are indebted to Carbide and Carbon Chemicals Corporation for a sample of this ester. [h] *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.81; H, 9.86. [i] Reported b. p. 162–164° at 16 mm. [Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., Vol. I, 1943, p. 7.] *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.39. Found: C, 68.66; H, 6.33. Copper salt m. p. 158–159°, reported m. p. 156° (Heilbron). A 38% yield of the β-keto ester was obtained when this condensation was carried out in liquid ammonia for thirty minutes. [j] See ref. 7. [k] See ref. 9. [l] Propionamide also obtained. [m] This product not obtained sufficiently pure for analysis. [n] Ethyl *n*-butyrate (23%) was recovered; *n*-butyramide also obtained. [o] Ethyl *i*-valerate (15%) was recovered; *i*-valeramide also obtained.

added with stirring and the ammonia replaced by ether.[5,6] With the drying tube attached to the condenser, the mixture was stirred and refluxed for ninety minutes and then poured onto crushed ice and acetic acid. The ether phase was washed with saturated sodium bicarbonate solution, dried and the solvent distilled. The residue was distilled *in vacuo* or recrystallized.

The results are summarized in Table I. The yields of β-keto ester are considered satisfactory with the alkyl acetates higher than ethyl acetate, with benzyl or α-phenylethyl acetate and especially with ethyl phenylacetate; some of the original ester was sometimes recovered but little if any of the corresponding amide was obtained. It has previously been shown that *t*-butyl acetate also is self-condensed satisfactorily by sodium amide.[9] These condensations may be represented as

$$2CH_3CO_2R + 2NaNH_2 \longrightarrow 2NH_3 + RONa + (CH_3COCHCO_2R)Na$$

$$2C_6H_5CH_2CO_2C_2H_5 + 2NaNH_2 \longrightarrow 2NH_3 + C_2H_5ONa + [C_6H_5CH_2COC(C_6H_5)CO_2C_2H_5]Na$$

Potassium amide previously has been found satisfactory for the self-condensations of α-phenylethyl acetate[7] and ethyl phenylacetate[9,10] and presumably it would also be applicable to the other condensations. The corresponding sodium alkoxides have been employed for the self-condensations of several alkyl acetates[11] and of ethyl phenylacetate[12] and, although the yields were better in certain cases, the reaction time was considerably longer. The condensation of benzyl acetate by sodium amide is especially interesting, since this ester fails to condense appreciably in the presence of sodium benzyloxide[13] and, when it is heated with sodium, a different type of reaction occurs to form β-phenylpropionic acid.[13,7]

It can be seen from Table I that, with ethyl propionate or ethyl *n*-butyrate, the yield of condensation product was lower than with the acetates and considerable amounts of the corresponding amides were obtained[14]; with ethyl *i*-valerate, only the amide was isolated.[15] Increasing the size or complexity of the alkoxy portion of these esters should increase the proportion of ester anion over the amide[8] but, since this should decrease the rate of self-condensation of the ester, a better yield of condensation product might not be realizable. Actually, the yield was less with *n*-butyl propionate than with ethyl propionate

(9) Shivers, Hudson and Hauser, THIS JOURNAL, **65**, 2051 (1943).

(10) This ester is also self-condensed in good yield by *i*-propylmagnesium bromide; Conant and Blatt, *ibid.*, **51**, 1227 (1929).

(11) Fisher and McElvain, *ibid.*, **56**, 1766 (1934).

(12) Roberts and McElvain, *ibid.*, **59**, 2007 (1937).

(13) See Bacon, *Am. Chem. J.*, **33**, 68 (1905).

(14) It is of interest that, even though the α-hydrogen of ethyl adipate might not be appreciably more reactive than the α-hydrogen of ethyl *n*-butyrate, the dicarboxylic ester is cyclized in good yield by sodium amide [Haller and Cornubert, *Bull. soc. chim.*, **4**, 39, 1626 (1926); *Compt. rend.*, **179**, 315 (1924)]. This intramolecular condensation is probably much more rapid than the intermolecular condensation of ethyl *n*-butyrate and it is possible that, with the latter ester, part of the ester anion formed initially is reconverted to the original ester, which is then converted irreversibly to *n*-butyramide (see note 6 of ref. 8).

(15) Ethyl propionate or ethyl *n*-butyrate is self-condensed in better yield using sodium ethoxide[2] although the reaction time is considerably longer than with sodium amide. Ethyl isovalerate fails to condense in the presence of sodium ethoxide[2] but it is condensed in good yield by sodium[2] or potassium triphenylmethide.[4]

(Table I). A better yield has been obtained with *t*-butyl *i*-valerate than with ethyl isovalerate but it was only 11% even after refluxing nine hours in benzene with potassium amide.[9] However, *t*-butyl esters of certain higher aliphatic acids may be acylated readily with *other* esters as described below.

Mixed-ester Condensations.—In order to minimize condensations other than the desired one we have employed as acylating esters ethyl nicotinate, which has no α-hydrogen, and certain phenyl esters, the carbonyl groups of which are considerably more reactive than the corresponding ethyl esters. Generally there has been used two equivalents each of sodium amide and ester acylated to one of the acylating ester, plus a 5% excess of sodium amide to minimize self-condensation of the ester acylated and an equal excess of the acylating ester.[16] The ester to be acylated has first been converted to its anion and the acylating ester then added.

Using the apparatus employed for the self-condensations, the ester to be acylated (0.40 mole) in an equal volume of dry ether was added to stirred sodium amide (0.42 mole) in 500 ml. of liquid ammonia. In general, the acylating ester (0.22 mole)[17] in an equal volume of dry ether was added immediately, the ammonia replaced by dry ether[5,6] and the stirred mixture refluxed for two hours. In acylations of the anion of ethyl phenylacetate,[18] the ammonia was replaced by ether and the acylating ester then added[19]; the stirred mixture was refluxed two hours.

In the acylations with the phenyl esters, the reaction mixture was poured onto ice and glacial acetic acid. The ether layer was separated and extracted with sodium bicarbonate solution followed by water. The ethereal solution was dried over drierite, the solvent distilled and the residue fractionated.

In the acylations with ethyl nicotinate, the mixture was poured onto ice and water, shaken thoroughly and the aqueous layer separated. While adding ice to the water solution, cold concentrated hydrochloric acid was added slowly until the solution was acidic. It was then saturated with sodium bicarbonate and the separated oil extracted with ether. The ethereal solution was dried over drierite, the solvent distilled and the residue fractionated.

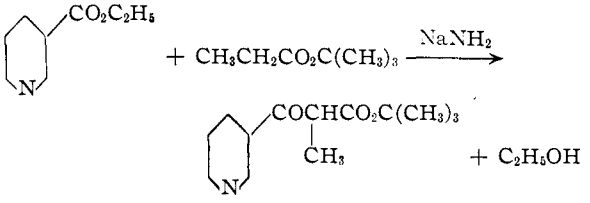
In the reaction with ethyl 2-phenylcinchoninate, the mixture was poured onto 200 ml. of cold 5% sodium hydroxide and thoroughly stirred. The ether phase was dried and the solvent distilled. The residue was washed with cold ethanol; it failed to melt up to 180° and left an ash on burning, being evidently the sodium derivative[20] of the β-keto ester (82%). Refluxing this derivative with glacial acetic acid for five minutes and filtering the hot solution onto ice produced a yellow oil, which was presumably the β-keto ester since on ketonic cleavage the corresponding ketone was obtained.

Most of the β-keto esters were cleaved to the corresponding ketones essentially as described previously[21] using 0.10 mole of the β-keto ester, 30 ml. of glacial acetic acid, 20 ml. of water and 3.75 ml. of concentrated sulfuric acid. The reaction mixture was cooled in an ice-bath and the excess acid neutralized with 20% sodium hydroxide or, in the cases with the nicotinyl ester, with sodium bicarbonate. The mixture was extracted several times with ether and the combined extracts dried over drierite. The solvent was distilled and the residue distilled *in vacuo* or recrystallized. The crude β-keto ester from ethyl 2-phenylcinchoninate was cleaved by heating it at 60–80° with 30% sulfuric acid. The yellow sulfate salt which precipitated on cooling was filtered off, suspended in water and neutralized with sodium carbonate. The ketone was filtered off and recrystallized from 95% ethanol.

The results are summarized in Table II. The yields of β-keto esters are considered satisfactory for the acylations of ethyl phenylacetate, *i*-propyl acetate and *t*-butyl propionate or *t*-butyl *n*-butyrate and fairly satisfactory for the acylations of *n*-butyl acetate, *i*-propyl propionate and ethyl succinate. However, the yield was poor with ethyl glutarate, while attempts to acylate ethyl α-methoxyacetate with phenyl benzoate produced mixtures of products. No attempt has been made to acylate ethyl propionate or ethyl *n*-butyrate with other esters, since it was assumed that the yields would not be satisfactory.[22] Although ester–alcohol exchange was possible in most of the condensations listed in Table II, none appeared to occur under the conditions employed. Examples of the condensations may be represented as

$$CH_3CO_2C_6H_5 + C_6H_5CH_2CO_2C_2H_5 \xrightarrow{NaNH_2} CH_3COCHCO_2C_2H_5 + C_6H_5OH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad C_6H_5$$

$$C_6H_5CO_2C_6H_5 + CH_3CO_2CH(CH_3)_2 \xrightarrow{NaNH_2} C_6H_5COCH_2CO_2CH(CH_3)_2 + C_6H_5OH$$



Since ester–alcohol exchange would probably occur, sodium alkoxides would presumably not be applicable for most of these acylations. Moreover, from the results in the literature, it appears that the corresponding acylations using the ethyl

(16) Using these proportions, isopropyl acetate has been acylated with phenyl benzoate in a 60% yield whereas using two equivalents of sodium amide to one each of ester acylated and of acylating ester, only a 16% yield has been obtained. For the influence of the proportions of reactants on the yields in the acylations and carbethoxylations of ketones, see refs. (5) and (6).

(17) In acylations with ethyl nicotinate, one-half quantities of reactants were used; in acylations with ethyl 2-phenylcinchoninate, one-quarter quantities of reactants were employed.

(18) When phenyl acetate was added directly to the anion of ethyl phenylacetate in liquid ammonia according to the more general procedure, only a low yield of the desired product was obtained. However, it is possible that the anion of ethyl phenylacetate may be acylated satisfactorily with phenyl benzoate using this procedure.

(19) When an attempt was made to acylate *i*-propyl acetate with phenyl benzoate by this procedure, the acetate self-condensed.

(20) Since this sodium derivative is soluble in ether and insoluble in water it probably has the chelate structure; its stability in the presence of water seems rather remarkable.

(21) Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941).

(22) Although ethyl caproate could probably not be acylated satisfactorily using sodium amide, ethyl ε-benzoylaminocaproate has been acylated in good yield with ethyl cinchoninate or ethyl quinolinate using this reagent [Ainley and King, *Proc. Roy. Soc.* London, **B125**, 60 (1938)]. In this special case, the amido hydrogen is probably first ionized, followed presumably by the ionization of the α-hydrogen in the ester end of the molecule.

TABLE II[a]

ACYLATION OF ESTERS USING SODIUM AMIDE AND KETONIC CLEAVAGE OF β-KETO ESTERS

Acylating ester	Ester acylated	β-Keto ester	B. p., °C.	Mm.	Yield[gg] %	Enol test[ff]	Ketone	B. p., °C.	Mm.	Yield[hh] %
Ph Ac	Et PhAc[b,c]	Et α-PhAcAc	140–144[d]	12	51	Deep violet	Methyl benzyl	97–100[u]	13	56
Ph Pr	Et PhAc[b,c]	Et α-PhPrAc	158–162[e]	18	55	Deep violet	Ethyl benzyl	112–115[v]	16	69
Ph Bz	Et PhAc[b,c]	Et α-PhBzAc	87–88 (m. p.)[f]		61	No enol	Benzyl phenyl	57–59 (m. p.)[w]		87
Et Nic	*i*-Pr Ac[c]	*i*-Pr NicAc	130–133[g]	1	64	Deep red	β-Pyridylmethyl	85–88[y]	5	75
Et Nic	*i*-Pr Pr	*i*-Pr NicPr	134–136[h]	3	36	Red	β-Pyridylethyl	96[aa]	5	34[z]
Et Nic	*t*-Bu Pr[c,i]	*t*-Bu α-NicPr	120–124[j,t]	1.5	54	Violet	β-Pyridylethyl	96–99[aa]	5	60
Et Nic	*t*-Bu *n*-Bu[i]	*t*-Bu α-Nic-*n*-Bu	132[k]	1.5	58	Light violet	β-Pyridyl *n*-propyl	107–111[bb]	6	48
Et 2-PhCin[l]	*i*-Pr Ac	*i*-Pr 2-Ph-Quin-4-Ac	.....	..	..	.....	2-Pbenyl-4-acetyl-quinoline	76–77 (m. p.)[cc]		57[z]
Ph Bz	*i*-Pr Ac	*i*-Pr BzAc	158–158.5[m]	15	60	Red	Metbyl phenyl	95–96[dd]	20	85
Ph Bz	*n*-Bu Ac	*n*-Bu α-BzAc	169–170[n]	11	32	Deep red	Methyl phenyl	93.5–94[dd]	20	71
Ph Bz	*i*-Pr Pr	*i*-Pr α-BzPr	151–155[o]	10	32	Amber	Ethyl phenyl	107–108[ee]	21	82
Ph Bz	*t*-Bu Pr[i]	*t*-Bu α-BzPr	151–155[p]	10	53	Violet	Ethyl phenyl	107[ee]	21	72
Et Nic	Et Succ	Et α-NicSucc	186–189[q,r]	3	33	Light red				
Et Nic	Et Glut	Et α-NicSucc	202–204[s]	5	8	Amber				

[a] Boiling and melting points are uncorrected. Analyses are by Arlington Laboratories, Fairfax, Virginia. [b] Acylating ester added to ether suspension of the sodium derivative of ethyl phenylacetate; see experimental. [c] Exactly two equivalents each of sodium amide and ester acylated to one of acylating ester were used. [d] *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.00; H, 7.12. Kimball, Jefferson and Pike, ref. 24, reported b. p. as 139–143° at 12 mm. [e] *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.72; H, 6.96. Dimroth and Feuchter [*Ber.*, **36,** 2243 (1903)] reported b. p. as 154–156° at 18 mm. [f] *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.31; H, 6.02. Walther and Schickler, [*J. prakt. Chem.*, [2] **55,** 318 (1897)], reported m. p. as 90°. We obtained an 89% yield of crude product melting at 84–87° before recrystallization from a mixture of alcohol and water. [g] *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.54; N, 6.76. Found: C, 63.30, 63.65; H, 6.54, 6.42; N, 7.02, 6.89. There was also isolated an 8% yield of *i*-propyl acetoacetate, b. p. 74–78° at 15 mm. [h] *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.89; H, 6.93; N, 6.61. [i] Prepared by the method of Abramovitch, Shivers, Hudson and Hauser, THIS JOURNAL, **65,** 986 (1943). [j] *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.29; N, 5.95. Found: C, 65.97; H, 7.12; N, 6.35. [k] *Anal.* Calcd. for $C_{14}H_{19}O_3N$: N, 5.75. Found: N, 5.99. [l] Prepared by the method of Doebner and Gieseke, *Ann.*, **242,** 291 (1887). [m] *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.21; H, 7.23. [n] *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.67; H, 7.57. *n*-Butyl acetate (16%), b. p. 120–125°, was recovered. [o] *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.87; H, 7.32. Found: C, 71.12; H, 7.47. *i*-Propyl propionate (28%), b. p. 107–109°, was recovered. [p] *Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.85; H, 7.65. *t*-Butyl propionate (9%), b. p. 115–120°, was recovered. [q] *Anal.* Calcd. for $C_{14}H_{17}O_5N$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.06; H, 6.11; N, 5.01. A 15% yield of the ethyl ester of cyclohexanedione-1,4-dicarboxylic acid-2,5, m. p. 124°, was obtained and 28% ethyl succinate, b. p. 107–108° at 10 mm., was recovered. [r] Distilled also at 168° at 1 mm. [s] *Anal.* Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 60.95; H, 6.54; N, 4.99. Ethyl glutarate (46%) was recovered. [t] Distilled also at 128° at 2 mm. [u] Barbier and Locquin, [*Bull. soc. chim.*, [4] **9,** 723 (1911)], reported b. p. as 104–106° at 13 mm. Purified methyl benzyl ketone prepared through the sodium bisulfite addition product boiled at 94–95° at 12 mm. (H. G. Walker of This Laboratory). [v] Reported b. p. 111° at 16 mm. [Ludlam, *J. Chem. Soc.*, **81,** 1189 (1902)]. [w] Reported m. p. 55–56° ["Organic Syntheses," **12,** 16 (1932)] and 60° [Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 365]. We obtained a quantitative yield of crude product, m. p. 50–55°, before recrystallization from 95% ethanol. [z] Over-all yield from original esters. [y] Reported b. p. 90–92° at 5 mm. [Strong and McElvain, THIS JOURNAL, **55,** 818 (1933)]. Phenylhydrazone, m. p. 138°; reported m. p. 134° and 137° [Hurd and Webb, *ibid.*, **49,** 551 (1927)]. [z] Obtained using 48% hydriodic acid for fifteen hours. When the ester was refluxed with acetic–sulfuric acid for five hours, no ketone was obtained, 53% of the ester being recovered. [aa] Phenylhydrazone, m. p. 144°; reported m. p. 145° [Engler, *Ber.*, **24,** 2539 (1891)]. [bb] Phenylhydrazone, m. p. 180°; reported m. p. 182°, (see ref. in note [aa]). [cc] Reported m. p. 75° [*Chem. Zentr.*, **93,** IV, 950 (1922)]. [dd] Reported b. p. 94.5° at 20 mm., Bruhl, *J. prakt. Chem.*, [2] **50,** 131 (1894). [ee] Reported b. p. 115–120° at 21 mm. [Heilbron, "Dictionary of Organic Compounds," Vol. II, Oxford University Press, New York, N. Y., 1938, p. 520]. 2,4-Dinitrophenylhydrazone, m. p. 190°; reported m. p. 190–191° [Huntress and Mulliken (see note [w]), p. 390]. [ff] Carried out by adding a drop of aqueous ferric chloride to an alcoholic solution of the β-keto ester. [gg] Yield based on one-half of the molar quantity of ester acylated; although all of the ester acylated is first converted to its anion one-half of it is regenerated (and presumably recoverable) when the β-keto ester is converted to its anion (see ref. 5). These yields are 10% higher than those calculated on the basis of the acylating ester when it is used in excess. [hh] Yield based on β-keto ester.

esters and sodium ethoxide produce lower yields,[23] except for the acylation of ethyl acetate with ethyl nicotinate. Our direct acetylation of ethyl phenylacetate to form ethyl α-phenylacetoacetate appears more convenient than the indirect method in "Organic Syntheses,"[24] involving the acetylation of phenylacetonitrile followed by alcoholysis.

It can be seen from Table II that good yields of ketones have generally been obtained on cleavage. The over-all yields from esters could probably be improved by cleaving the crude β-keto esters; the method appears to be useful for the preparation of certain of the ketones.

(23) For example, there has been reported a 37% yield for the acylation of ethyl acetate with ethyl benzoate and only a 19% yield for the acylation of ethyl propionate with ethyl benzoate (Dorsch and McElvain, THIS JOURNAL, **54,** 2960 (1932)). Apparently the acylation of ethyl propionate or ethyl *n*-butyrate with ethyl nicotinate using sodium ethoxide has not been reported but the corresponding acylations with ethyl picolinate which is considered even more reactive appear to have produced only poor yields (Pinner, *Ber.*, **33,** 1230 (1900); **34,** 4234 (1901)). For a review of the literature on acylations with nitrogen heterocyclic esters see Koelsch, *J. Org. Chem.*, **10,** 34 (1945).

(24) Julian, Oliver, Kimball, Pike and Jefferson, "Organic Syntheses," John Wiley and Sons, New York, N. Y., Coll. Vol. II, 1943, p. 487; Kimball, Jefferson and Pike, *ibid.*, 1943, p. 284.

Summary

1. The suitability of sodium amide for effecting the Claisen acylation of esters has been studied. Various self and mixed-ester condensations have been effected satisfactorily using this reagent. The results are compared with analogous cases using sodium alkoxides.

2. The β-keto esters from the mixed-ester condensations have been cleaved to the corresponding ketones.

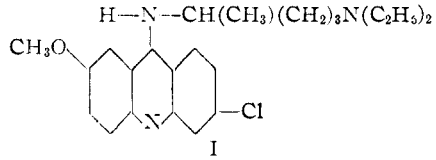
DURHAM, N. C. RECEIVED JULY 29, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

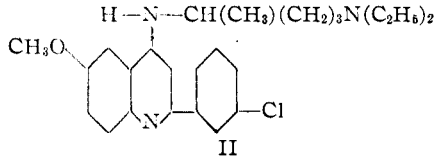
Some 7-Chloroquinolines Patterned as "Open Models" of Atebrin

BY HENRY GILMAN AND ROBERT A. BENKESER

In earlier papers[1] the syntheses of several "open models" of atebrin (I) were described.



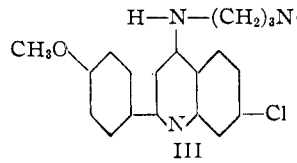
I



II

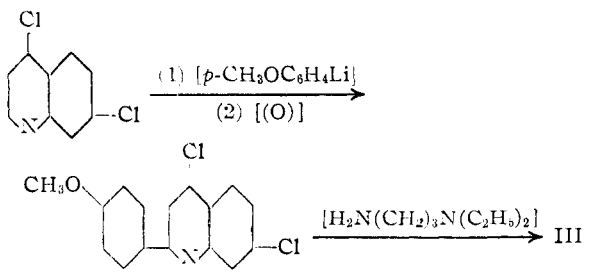
One[1a] of these (II) has a chlorophenyl group in place of the fused chlorobenzo group in atebrin.

It appeared particularly appropriate, in extension of these studies, to open the opposite benzo group of (I) to obtain a homolog like 2-*p*-methoxyphenyl - 7 - chloro - 4 - (3 - diethylaminopropylamino)-quinoline (III).



III

The synthesis of this compound was accomplished by the following sequence of reactions



The intermediate dihydro compound was oxidized by picric acid, and the picrate was incidentally helpful in isolating the product. It is interesting to note in connection with the RLi reaction that the 4-chlorine in the quinoline which is sufficiently reactive to undergo condensation with 3-diethylaminopropylamine, but relatively unreactive toward the RLi compound, does not show any deactivating effect on the anil linkage.[2]

Because a nuclear methyl group or a chlorine is effective in some types[1a] examined for experimental avian malaria, a related series of reactions was used for the preparation of 2-*p*-tolyl-7-chloro-4-(3-diethylaminopropylamino)-quinoline and of 2-*p*-chlorophenyl-7-chloro-4-(3-diethylaminopropylamino)-quinoline. The *p*-chlorophenyllithium was prepared by a halogen-metal interconversion reaction[3] between *p*-chlorobromobenzene and *n*-butyllithium.

In extension of studies of some compounds with sulfur-containing side-chains,[4] 2-phenyl-7-chloro-4-quinolyl 2-diethylaminoethyl sulfide was synthesized from 2-phenyl-4,7-dichloroquinoline and sodium 2-diethylaminoethyl mercaptide. The simple, unsubstituted 2-phenyl compound was used because such types are known to be effective occasionally.[1a]

Experimental

2-Aryl-4,7-dichloroquinolines.—In a typical experiment, there was added with stirring to 32 cc. of a solution containing 0.034 mole of phenyllithium cooled to 0°, 5 g. (0.026 mole) of 4,7-dichloroquinoline in 60 cc. of ether cooled in an ice-bath. The addition was complete in three and one-half minutes; the solution was stirred an additional two and one-half minutes; and hydrolysis was effected by the addition of 30 cc. of water. The ether layer was separated, dried, the solvent was removed under reduced pressure; the red, oily residue was dissolved in a small volume of 95% ethanol, and this solution was added to a hot solution of 7 g. of picric acid in 40 cc. of 95% ethanol. The solid, red picrate which precipitated immediately was filtered, dried, and decomposed by refluxing fifteen minutes with 1:1 ammonium hydroxide. The dark red solution was filtered while still hot, and after washing the dark brown precipitate several times with warm water it was crystallized from 95% ethanol (with the use of Norit) to yield 2.5 g. (35%) of 2-phenyl-4,7-dichloroquinoline melting at 99–100°.

Table I contains the 2-aryl-4,7-dichloroquinolines prepared by this general procedure.

(1) (a) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944); (b) Gilman, Christian and Spatz, *ibid.*, **68**, 979 (1946); Gilman, Towle and Spatz, *ibid.*, **68**, 2017 (1946).

(2) Gilman and Spatz, *ibid.*, **62**, 446 (1940); **63**, 1553 (1941).

(3) Gilman, Langham, and Moore, *ibid.*, **62**, 2327 (1940); Langham, Brewster, and Gilman, *ibid.*, **63**, 545 (1941); Gilman, Langham, and Jacoby, *ibid.*, **61**, 106 (1939); Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(4) Gilman and Woods, THIS JOURNAL, **67**, 1843 (1945); Gilman and Tolman, *ibid.*, **67**, 1847 (1945).