Conjugate Addition Reactions of Ethyl Atropate with Certain Alkali Nucleophiles. Alkylations[1a]

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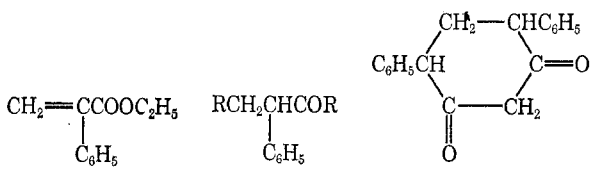
Ethyl atropate, $CH_2{=}C(C_6H_5)COOC_2H_5$, underwent conjugate addition with phenylmagnesium bromide and with alkali di- and triphenylmethides to form corresponding β-substituted products. Ethyl atropate also underwent conjugate additions with the 1,2-dialkali salts of benzophenone and benzophenone anil to afford a lactone and a γ-amino ester, respectively. Several new β-amino esters were prepared by similarly condensing ethyl atropate with certain alkali amides or with appropriate free amines. Various alkylations of intermediate carbanions were effected to afford α-substituted derivatives. Some related reactions were also realized.

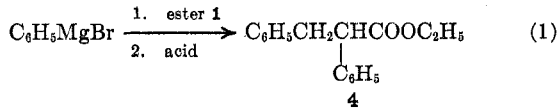
Methyl atropate and ethyl atropate (**1**) have previously been shown to undergo polymerization with catalytic amounts of various nucleophiles, including sodium amide,[2] alkali triphenylmethide,[2] *n*-butyllithium,[3,4] and *n*-butylmagnesium bromide.[4] Most of these reactions presumably involved a series of conjugate 1,4 additions of the ester, first with the nucleophile and then with intermediate carbanions. However, only two types of reactions of these esters with 1 molar equiv or more of nucleophiles appear to have been reported previously. One type involved methyl atropate with methyl- or phenylmagnesium halide to form ketone **2a** or **b**;[5] the other involved ethyl atropate (**1**) with phenylacetone in the presence of sodium ethoxide to give cyclic β diketone **3**.[6] Apparently, the first type of reaction involved both 1,2 and 1,4 additions, and the second both Michael and Dieckmann condensations.



1 **2a**, R = CH_3; **b**, R = C_6H_5 **3**

In the present investigation, ethyl atropate (**1**) was found to undergo single conjugate addition reactions with several types of nucleophiles to furnish useful methods of synthesis of a number of monomeric products.

Results with Carbanions.—In contrast to methyl atropate,[5] **1** underwent 1,4 addition with phenylmagnesium bromide at room temperature to form **4** in 32–58% yield (eq 1).



(1)

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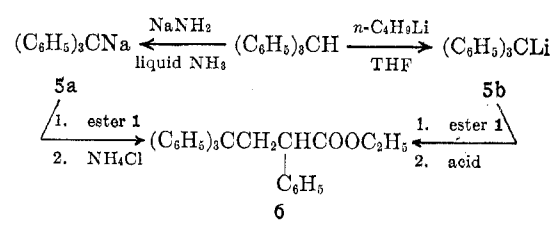
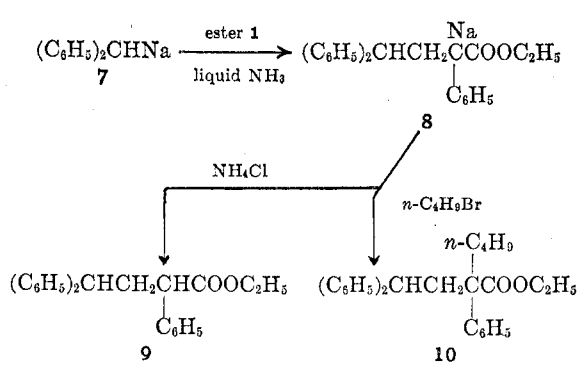
Although ester **1** has been reported to produce polymers with catalytic amounts of alkali triphenylmethides **5a** or **b**,[2] **1** afforded the monomeric β-trityl derivative **6** with 1 molar equiv of these reagents in liquid ammonia or tetrahydrofuran (THF); the yields of **6** were 40 and 66%, respectively (Scheme I).

SCHEME I



Similarly, ester **1** was condensed with sodium diphenylmethide (**7**) in liquid ammonia to form the β-diphenylmethyl derivative **9** in 61% yield. That sodium adduct **8** was present in the reaction mixture before neutralization was shown by *in situ* alkylation with *n*-butyl bromide to give the α-*n*-butyl derivative **10** in 38% yield (Scheme II).

SCHEME II



Ester **1** underwent conjugate addition, accompanied by cyclization, with disodium salt **11** to form lactone **13** in 37% yield; presumably, disodium adduct **12** was an intermediate (Scheme III). However, it was not established whether the cyclization occurred before or after neutralization.

Similarly, ester **1** was condensed with dialkali salts **14a** or **b** in liquid ammonia to give γ-amino ester **15** in 20–30% yield. None of the corresponding cyclic lactam was isolated.

(1) (a) Supported at the University of Missouri by the Petroleum Research Fund, administered by the American Chemical Society, and at Duke University by the Office of Army Research (Durham); (b) University of Missouri; (c) Duke University; (d) Union Carbide Corp., South Charleston, W. V.

(2) C. de Saint-Gobain, French Patent 1,357,679 (1964); *Chem. Abstr.*, **61**, 12167*d* (1964).

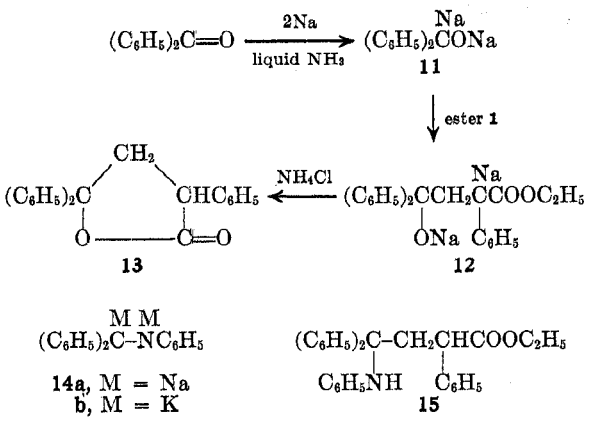
(3) H. Hopff, H. Luessi, and L. Borla, *Makromol. Chem.*, **81**, 268 (1965); *Chem. Abstr.*, **62**, 13250*a* (1965).

(4) K. Chikanishi and T. Tsuruta, *Makromol. Chem.*, **73**, 231 (1964); *Chem. Abstr.*, **61**, 728*g* (1964).

(5) A. McKenzie and E. R. Winton, *J. Chem. Soc.*, 840 (1940).

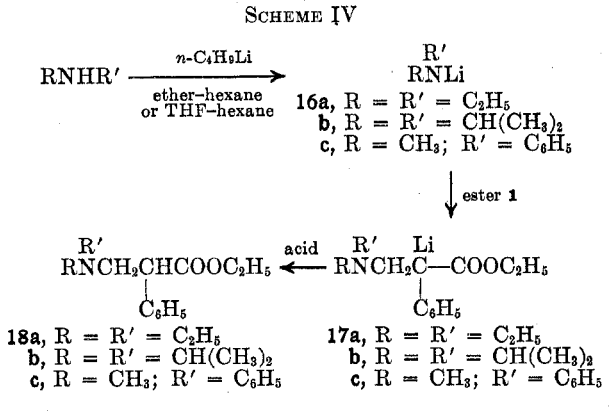
(6) G. R. Ames and W. Davey, *ibid.*, 1794 (1958).

SCHEME III

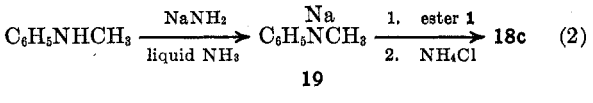


Results with Anions of Amines.—Similar to the previously reported polymerization of ester **1** with a catalytic amount of sodium amide in THF, anisole, and dimethyl sulfoxide,[2] we observed some polymerization of **1** even with 1 molar equiv of alkali amides in liquid ammonia and with lithioethylamide in ether–hexane or THF–hexane. More significantly, however, single conjugate addition reactions were realized with ester **1** and 1 molar equiv of the lithio derivatives of secondary amines, **16a–c**, in ether–hexane or THF–hexane to form β-dialkylamino esters **18a–c** in yields of 62, 33, and 48–54%, respectively (Scheme IV). That lithio adduct **17** was present in the reaction mixture before neutralization was shown by *in situ* alkylation with benzyl chloride to form the α-benzyl derivative **21a**.

SCHEME IV



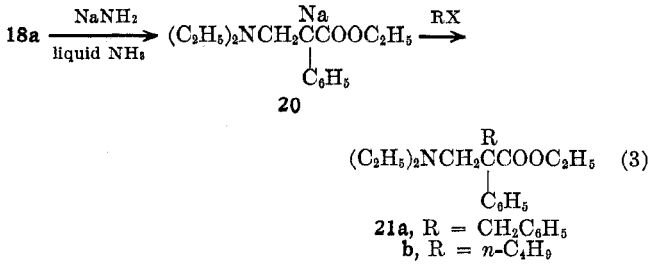
β-Amino ester **18c** was also prepared through sodium methylaniline (**19**) in liquid ammonia, the yield being 66% (eq 2). This method, however, does not appear



(2)

suitable for the two purely aliphatic amines, with which the equilibrium of the acid–base reaction would presumably be on the side of the free amine and sodium amide.

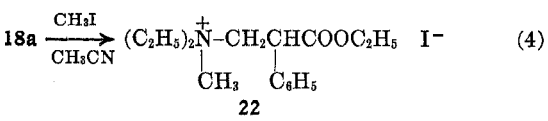
β-Amino ester **18a** was alkylated at its α carbon with certain halides by means of sodium amide in liquid ammonia. Thus, the intermediate sodium salt **20** underwent alkylation with benzyl chloride and *n*-butyl bromide to form the α-alkyl derivatives **21a** and **b** in yields of 71 and 75%, respectively (eq 3).



(3)

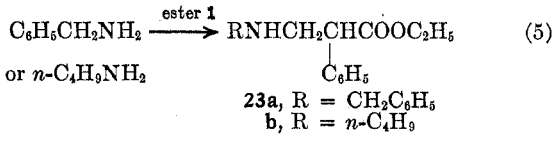
At least for the preparation of **21a**, this sodium amide method seems preferable to the above-mentioned *in situ* benzylation of the lithium adduct **17a**, which required a relatively longer reaction period for a satisfactory yield (see Scheme IV and Experimental Section).

Also, β-amino ester **18a** was methylated at its nitrogen atom with methyl iodide in acetonitrile to form the quaternary ammonium iodide **22** in 80% yield (eq 4).



(4)

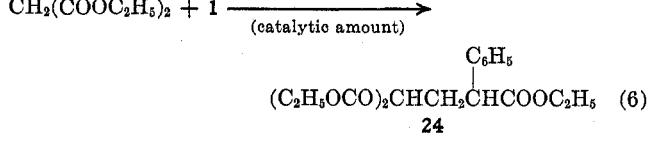
Results with Free Amines and Basic Catalysis.—Ester **1** underwent an uncatalyzed conjugate addition reaction with benzylamine and *n*-butylamine in ethanol to form the β-amino derivatives **23a** and **b** in yields of 71 and 50%, respectively (eq 5).



(5)

Although this method would presumably be suitable with certain other primary amines, it failed with free diethylamine. Even in the presence of catalytic amounts of sodium ethoxide, sodium methoxide, or *n*-butyllithium, ester **1** underwent only a little conjugate addition with diethylamine and methylaniline to form β-amino esters **18a** and **c**, respectively.

Results with Malonic Ester.—Ester **1** underwent a typical Michael condensation with ethyl malonate in the presence of a catalytic amount of sodium ethoxide or sodium methoxide neat or in ethanol to form the β derivative **24** in 55–60% yield (eq 6).



(6)

When malonic ester was converted into its sodium salt with 1 molar equiv of sodium ethoxide in ethanol or sodium amide in liquid ammonia and ester **1** was added, the yields of **24** were only 5 and 24%, respectively.

Discussion

Interestingly, in spite of the tendency of ester **1** to be polymerized by strong nucleophiles, the reactions described herein stopped at the initial stage to form mono-

mers with most of the nucleophiles studied. Since even 1 molar equiv of alkali amides and lithium derivatives of primary amines afforded polymeric material, success in arresting the present reactions at the monomeric stage with the alkali derivatives of secondary amines may be ascribed to a steric factor. Possibly a steric factor was instrumental also in the success of the preparation of monomers with the alkali derivatives of the polyphenyl compounds.

With the exceptions of the Grignard and malonic ester derivatives, **4** and **24**, respectively, all of the products described in this paper appear to be new. Their structures were supported by elemental analyses and absorption spectra (see Experimental Section).

Although **4** can be prepared more conveniently by alkylation of sodium ethyl phenylacetate,[7] **24** seems better prepared by the present method than by an earlier one involving alkylation of sodium malonic ester with 2-phenyl-3-chloropropionate, for which no yield was reported.[8] The latter reaction may have been accompanied by dehydrohalogenation, a type of reaction that occurred exclusively in an attempt to alkylate potassium diphenylmethide with ethyl 3-bromopropionate.[9]

While there appear to be no earlier examples for conjugate additions of an α,β-unsaturated ester with an alkali derivative of a secondary amine, such reactions with the other types of nucleophiles have been described previously. Thus, besides the well-known Grignard and Michael types of reactions, conjugate additions of ethyl cinnamate with potassium diphenylmethide,[10] of chalcone with disodium salt **11**,[11] and of methyl or ethyl acrylate with primary or secondary amines[12] have been reported. Similar to our observation with ester **1** and free diethylamine (see above), ethyl cinnamate has been reported not to react with this amine.[13]

The present results, as well as earlier ones, fit into two categories with regard to affecting satisfactorily conjugate addition reactions of α,β-unsaturated esters (or other such systems) with nucleophiles: (a) those that form a sufficiently more stable (more weakly basic) adduct carbanion; and (b) those that produce a more thermodynamically stable nuetral adduct compared to the two starting neutral components. Category a includes the reactions of Grignard reagents, the polyphenyl carbanions, and the anions of amines, though the magnesium of the Grignard reagent may also play an important role.[14] Category b includes the reactions of the neutral free amines and the base-catalyzed Michael condensations.

Apparently, the equilibrium of the conjugate addition reaction of ester **1** with a free secondary amine, *e.g.*, diethylamine, is on the side of the secondary amine, since **1** failed to react satisfactory with diethylamine even in the presence of catalytic amounts of sodium ethoxide or other basic reagents. Also, β-amino ester **18c** was found to undergo cleavage with a catalytic quantity of sodium ethoxide in ethanol to form methylaniline and ethyl atropate (**1**), though the equilibrium may have been shifted in favor of these components by polymerization of most of **1** (see Experimental Section). Therefore, the satisfactory conjugate additions of **1** with the alkali derivatives of the secondary amines appear attributable to formation of the more weakly basic adduct anion such as **17**, although the metallic cation may also be influential, especially when it is lithium.[14]

On the other hand, the equilibrium of the conjugate addition reaction of ester **1** with malonic ester is evidently on the side of the neutral adduct **24**, since **24** was obtained in good yield with a catalytic amount of sodium ethoxide but not with 1 equiv of this base. Thus, conjugate addition reactions of ester **1** with malonic ester occur better with a catalytic amount than with 1 equiv of sodium ethoxide, since the resulting adduct carbanion, which is a stronger base than the malonic ester carbanion, needs to acquire a proton to afford the more thermodynamically stable netural adduct.

Experimental Section[15]

Preparation of Ethyl Atropate (**1**).—This ester was prepared by a modification of the procedure of Ames and Davey.[6] Sodium ethoxide (2.27 mol), prepared in 1200 ml of anhydrous xylene from 105.8 g (2.3 mol) of ethanol and 52.2 g (2.27 g-atoms) of sodium, was treated with 328.5 g (2.25 mol) of diethyl oxalate, followed by 489.0 g (2.98 mol) of ethyl phenylacetate. Each addition required 30 min, and the temperature was maintained below 35° with a water bath. The solution was allowed to stand overnight, and the yellow solid which precipitated was collected under suction and washed with ether until the ether washings were colorless. The solid was then slurried with 1 l. of ether and made acidic by the addition of 1 *N* hydrochloric acid. The resulting phases were separated, the aqueous phase was extracted with two 300-ml portions of ether, and the ether extracts were combined and concentrated under reduced pressure. The remaining oil was treated with 300 ml of 38% aqueous formaldehyde and 1 l. of water. The resulting rapidly stirred mixture was then treated at 12–18° during 3 hr with a solution of 243.0 g (1.76 mol) of potassium carbonate in 450 ml of water, and stirred for an additional 4 hr. The organic phase was extracted with 1 l. of ether and the aqueous phase was extracted with two 300-ml portions of ether. Work-up followed by distillation of the crude product on a 40 theoretical plate spinning-band distillation column afforded 230 g (58%) of ethyl atropate (**1**), bp 88–91° (2.5 mm) [lit.[6] bp 76–77° (1.2 mm)]. The nmr of the product showed the presence of 97.5% ethyl atropate and 2.5% ethyl phenylacetate. Ethyl atropate could be preserved without the presence of polymerization inhibitors by refrigerator storage under a nitrogen atmosphere.

Purer ethyl atropate (**1**) was realized in 65% yield when the preparation was repeated employing 2.25 mol each of ethyl phenylacetate and diethyl oxalate along with 2.5 mol of sodium ethoxide.

Addition of Phenylmagnesium Bromide to Ethyl Atropate.—Phenylmagnesium bromide, prepared from 0.60 g (0.025 g-atom) of magnesium and 3.93 g (0.025 mol) of bromobenzene in 50 ml of ether, was treated during 12 min with a solution of 4.4 g

(7) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(8) V. Breznak, *Biochem. Z.*, **205**, 417; Beilsteins Handbuch ser organischen chemie, Vol. 9, II, Springer-Verlag, 1944, p 715.

(9) See W. G. Kofron and N. I. Gottfried, *J. Org. Chem.*, **31**, 3426 (1966).

(10) M. T. Tetenbaum and C. R. Hauser, *ibid.*, **23**, 229 (1958).

(11) See P. J. Hamrick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 493 (1959).

(12) R. Mozingo and J. H. McCracken, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 258.

(13) K. Morsch, *Monatsh. Chem.*, **61**, 229 (1932).

(14) For the metallic cation effect in carbonyl addition reactions, see W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, **26**, 2306 (1961).

(15) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin–Elmer Infracord Model 137 either neat, as Nujol mulls, or in KBr disks. Nmr spectra were obtained with a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Triangle Chemical Laboratories, Chapel Hill, N. C. Unless indicated, the reactions were worked up by extracting the aqueous phase with three or four 50-ml portions of ether, drying ($CaSO_4$ or $MgSO_4$), and concentrating the combined extracts on the rotary evaporator.

(0.025 mol) of ethyl atropate (1) in 50 ml of ether. After 5 hr, the white suspension was cooled to 0° and hydrolyzed by 100 ml of 3 *N* hydrochloric acid. Work-up[15] and distillation of the resulting residue afforded 2.0 g (32%) of ethyl 2,3-diphenylpropanoate (4), bp 168–170° (4 mm) [lit.[7] bp 115–116.5° (0.13 mm)].

Similarly, addition of a twofold excess of phenylmagnesium bromide to 0.025 mol of ethyl atropate for 16 hr gave ester 4 in 58% yield. Saponification of a portion of ester 4 according to published procedures[7] afforded the expected 2,3-diphenylpropanoic acid, mp 83–84° (lit.[7] mp 84–85°).

Addition of Triphenylmethane to Ethyl Atropate. A. By Means of Sodium Amide in Liquid Ammonia.—To 0.027 mol of sodium amide in 300 ml of anhydrous liquid ammonia,[16] prepared from 0.64 g (0.027 g-atom) of sodium, was added 6.7 g (0.027 mol) of solid triphenylmethane, followed after 30 min by a solution of 4.4 g (0.025 mol) of ethyl atropate in 50 ml of ether added during 10 min. The reaction mixture was treated immediately with 20 g of solid ammonium chloride and the ammonia was allowed to evaporate. The resulting residue was hydrolyzed by 100 ml of 3 *N* hydrochloric acid. Work-up[15] afforded a gumlike material which was crystallized from 95% ethanol to afford 4.2 g (40%) of ethyl 2,4,4,4-tetraphenylbutanoate (6): mp 125–128°; ir (KBr) 1730 (C=O), 770, 747, and 695 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.25 (d, 20 ArH), 3.5 (m, 5, CH, CH_2), and 0.9 (t, 3, CH_3).

Anal. Calcd for $C_{30}H_{28}O_2$: C, 85.80; H, 6.77. Found: C, 85.45; H, 6.82.

B. By Means of *n*-Butyllithium.—To a solution of 4.88 g (0.02 mol) of triphenylmethane in 50 ml of THF and 25 ml of ether was added, during 5 min, 20 ml (0.03 mol) of 1.6 *M* *n*-butyllithium in hexane.[17] After the solution was stirred for 4 hr at 0° (ice bath), the bright red suspension was treated with a solution of 3.6 g (0.02 mol) of ethyl atropate in 20 ml of THF. After 30 min, the resulting clear red solution was poured into 300 ml of ice–water. Work-up[15] gave 5.8 g of ester 6, mp 125–128°; recrystallization from 95% ethanol afforded 5.5 g (66%) of this compound, mp 126–128°.

Addition of Sodium Diphenylmethane to Ethyl Atropate.—This reaction was effected essentially as described above for sodium triphenylmethane employing 0.025 mol of sodium amide,[16] 4.2 g (0.025 mol) of diphenylmethane, and 4.4 g (0.025 mol) of ethyl atropate. Distillation of the crude product gave 5.21 g (61%) of ethyl 2,4,4-triphenylbutanoate (9): bp 203–204° (2 mm); ir (neat) 1720 (C=O), 752, and 708 cm^{-1} (ArH); nmr (CCl_4) δ 7.08 (d, 15, ArH), 3.9 (q, 2, OCH_2), 2.93 (m, 4, CH, CH_2), and 1.04 (t, 3, CH_3).

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.88; H, 6.99. Found: C, 84.00; H, 7.09.

***In situ* Butylation of the Diphenylmethyl Adduct of Ethyl Atropate.**—This reaction was accomplished essentially as described in the preceding experiment, except that as soon as the addition of the ethyl atropate was completed, the reaction mixture was treated during 2 min with a solution of 3.45 g (0.025 mol) of *n*-butyl bromide in 50 ml of ether. After 1 hr, the mixture was neutralized by the addition of 10 g of solid ammonium chloride. Work-up[15] afforded 3.75 g (38%) of 1,1,3-triphenyl-3-carbethoxyheptane (10): bp 239–240° (1 mm); ir (neat) 1720 (C=O), 752, and 708 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.2 (m, 15 ArH), 3.8 (m, 3, OCH_2, Ar_2CH), 3.0 (m, 2, CH_2), 1.9 (m, 2, CH_2), and 0.89 (m, 10, CH_2, CH_3).

Anal. Calcd for $C_{28}H_{32}O_2$: C, 84.00; H, 8.00. Found: C, 84.01; H, 8.24.

Addition of Disodium Benzophenone (11) to Ethyl Atropate.—To 250 ml of liquid ammonia was added 1.15 g (0.05 g-atom) of sodium metal followed by a solution of 4.55 g (0.025 mol) of benzophenone in 30 ml of ether. The resulting purple solution was stirred for 10 min and then treated during 2 min with a solution of 4.4 g (0.025 mol) of ethyl atropate in 25 ml of ether. The resulting ink-blue solution was stirred for 2 min and poured into 200 ml of ammonia containing 10 g of ammonium chloride. The ammonia was allowed to evaporate from the yellow solution and the residue was hydrolyzed by 100 ml of 3 *N* hydrochloric acid. Solid which did not dissolve was combined with that obtained by evaporating the ether from three extractions of the aqueous phase. Recrystallization of the solid from ethyl acetate gave 2.85 g (37%) of 2,4,4-triphenylbutyrolactone (13): mp 159–162°; ir (Nujol) 1760 (C=O) and 700 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.0 (m, 15, ArH) and 3.3 (m, 3, CH, CH_2).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.07; H, 5.73. Found: C, 84.16; H, 5.77.

Benzophenone (1.85 g, 21%) was recovered from the reaction mixture and isolated as its 2,4-dinitrophenylhydrazone derivative, mp and mmp 238–240°.

Addition of Dialkalibenzophenone Anil to Ethyl Atropate.—This reaction was effected essentially as described above for disodium benzophenone by adding 6.43 g (0.025 mol) of solid benzophenone anil in small portions to an ammonia solution of 1.15 g (0.05 g-atom) of sodium followed by a solution of 4.4 g (0.025 mol) of ester 1 in 50 ml of ether. Work-up[15] afforded an insoluble solid that was collected and treated with aqueous sodium hydroxide. Further work-up[15] afforded, upon recrystallization from absolute ethanol, 3.3 g (30%) of ethyl 2,4,4-triphenyl-4-phenylaminobutanoate (15): mp 140.5–142.5°; ir (Nujol) 3150 (NH), 1700 (C=O), 710, and 690 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.37 (m, 20, ArH), 6.4 (s, 1, NH), 3.25 (m, 5, CH, CH_2), and 1.05 (t, 3, CH_3).

Anal. Calcd for $C_{30}H_{29}NO_2$: C, 82.75; H, 6.66; N, 3.21. Found: C, 82.63; H, 6.65; N, 3.16.

When the reaction was repeated employing 1.95 g (0.05 g-atom) of potassium metal, γ-amino ester 15 was obtained in 20% yield.

Addition of N-Lithioamides to Ethyl Atropate. A. General Procedure.—To a solution of 0.025 or 0.05 mol of the appropriate amine in 100 ml of anhydrous ether was added 17.3 or 34.5 ml (0.027 or 0.055 mol) of 1.6 *M* *n*-butyllithium in hexane.[17] After 15–60 min, the reaction mixture was treated during 30 min with a solution of 4.4 or 8.8 g (0.025 or 0.05 mol) of ethyl atropate in 50 ml of ether. The resulting yellow solution was stirred for 5 hr at 25°, and then treated with 100 ml of 3 *N* hydrochloric acid The aqueous phase was extracted with three 50-ml portions of ether, which were discarded. The aqueous phase was neutralized by solid Na_2CO_3 and worked up,[15] and the crude product was distilled.

B. Diethylamine.—This reaction was effected on a 0.05-mol scale to afford 7.63 g (62%) of ethyl 2-phenyl-3-diethylaminopropanoate (13a): bp 115–116° (2.5 mm); ir (neat) 1740 (C=O), 733, and 700 cm^{-1} (ArH); nmr (neat) δ 7.2 (m, 5, ArH), 3.25 (m, 9, all CH_2, CH), 1.05 (t, 6, CH_3), and 0.93 (t, 3, CH_3).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.38; H, 9.20; N, 5.96.

When the reaction was repeated essentially as described above employing THF as the solvent rather than ether, amino ester 18a was obtained in 48% yield.

C. Diisopropylamine.—Similarly, 0.05 mol of the appropriate reagents afforded 4.6 g (33%) of ethyl 2-phenyl-3-diisopropylaminopropanoate (18b): bp 142–144° (2 mm); ir (neat) 1740 (C=O), 732, and 699 cm^{-1} (ArH); nmr (neat) δ 7.1 (m, 5, ArH), 3.3 (m, 7, CH_2, CH), and 0.9 (m, 15, CH_3).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.63; H, 9.75; N, 5.05. Found: C, 73.59; H, 9.84; N, 5.24.

D. N-Methylaniline.—Likewise, 0.025 mol of the appropriate reagents gave 3.23 g (48%) of ethyl 2-phenyl-3-N-methylanilinopropanoate (18c): bp 160–161° (2 mm); ir (neat) 1730 (C=O), 758, and 695 cm^{-1} (ArH); nmr ($CDCl_3$) δ 6.9 (m, 10, ArH), 3.9 (m, 5, OCH_2, CH_2CH), 2.8 (s, 3, NCH_3), and 1.3 (t, 3, CH_3).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.13; H, 7.55; N, 4.92.

Addition of N-Methylaniline to Ethyl Atropate By Means of Sodium Amide in Liquid Ammonia.—To 0.025 mol of sodium amide in 300 ml of liquid ammonia[16] was added a solution of 2.675 g (0.025 mol) of N-methylaniline in 25 ml of ether. After 15 min, the resulting green suspension was treated during 20 min with a solution of 4.4 g (0.025 mol) of ethyl atropate in 100 ml of ether. After the mixture was stirred for 4 hr, the now gray suspension was neutralized by 15 g of solid ammonium chloride and the ammonia was allowed to evaporate. Work-up[15] gave 4.65 g (66%) of β-amino ester 18c, bp 160–161° (2 mm).

***In situ* Benzylation of Lithium Ethyl 2-Phenyl-3-diethylaminopropanoate (17a).**—Lithium salt 17a, prepared as above, was treated during 10 min with a solution of 6.33 g (0.05 mol) of benzyl chloride in 50 ml of ether. Heat was applied and the yellow mixture was refluxed for 17 hr. Upon cooling, the mixture was hydrolyzed and worked up[15] to afford 3.59 g (29%) of recovered ethyl atropate, bp 115–118° (3 mm), and 4.85 g (28%) of ethyl 2-benzyl-2-phenyl-3-diethylaminopropanoate (21a):

(16) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(17) Supplied by the Foote Mineral Co., Exton, Pa.

bp 179–180° (3.5 mm); ir (neat) 1725 (C=O), 740, and 705 cm^{-1} (ArH); nmr (neat) δ 7.15 (s, 5, ArH), 7.0 (s, 5, ArH), 4.0 (q, 2, OCH_2), 3.51 (s, 2, $ArCH_2$), 3.1 (s, 2, $ArCCH_2N$), 2.4 (q, 4, NCH_2), and 0.9 (m, 9, CH_3).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.56; H, 8.52; N, 4.28.

When the reaction was repeated by refluxing the reaction mixture for 50 hr instead of 17 hr, amino ester **21a** was obtained in 50% yield.

Alkylations of Ethyl 2-Phenyl-3-diethylaminopropanoate (18a) by Means of Sodium Amide in Liquid Ammonia. A. Benzyl Chloride.—To a suspension of 0.0275 mol of sodium amide in 300 ml of liquid ammonia[15] was added during 5 min a solution of 6.125 g (0.025 mol) of amino ester **18a** in 50 ml of ether. After 30 min, the resulting pale green solution was treated during 5 min with a solution of 3.16 g (0.025 mol) of benzyl chloride in 50 ml of ether. After 4 hr, the mixture was treated with 15 g of solid ammonium chloride and the ammonia was allowed to evaporate. The resulting residue was worked up[15] to afford 6.0 g (71%) of benzyl derivative **21a**, bp 162–163° (2 mm).

B. *n*-Butyl Bromide.—This reaction was accomplished essentially as described in part A above by employing 3.43 g (0.025 mol) of *n*-butyl bromide to afford 5.69 g (75%) of ethyl 2-*n*-butyl-2-phenyl-3-diethylaminopropanoate (**21b**): bp 126–128° (1 mm); ir (neat) 1725 (C=O), 755, and 705 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.2 (s, 5, ArH), 4.1 (q, 2, OCH_3), 3.04 (d, 2, NCH_2CAr), 2.34 (q, 4, NCH_2), and 1.0 (m, 18, CH_2, CH_3).

N-Methylation of Amino Ester 18a.—To a solution of 10.0 g (0.041 mol) of amino ester **18a** in 100 ml of acetonitrile was added 20 g of methyl iodide. Sufficient heat was applied to the reaction mixture to cause gentle reflux. After 24 hr, the solution was allowed to cool before it was poured into 750 ml of ether. The resulting precipitate was collected and recrystallized from acetonitrile–ether to afford 12.85 g (80%) of (2-carbethoxy-2-phenyl)-ethyl diethyl methyl ammonium iodide (**22**): mp 122–124°; ir (Nujol) 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.43 (m, 5, ArH), 4.0 (m, 9, CH_2, CH), 3.26 (s, 3, NCH_3), 1.38 (t, 6, CH_3), and 1.2 (t, 3, CH_3).

Anal. Calcd for $C_{16}H_{26}NO_2I$: N, 3.57. Found: N, 3.45.

That **22** was the actual structure of this quaternary salt was fruther demonstrated by effecting a β elimination on it by lithium diethylamine to give ethyl atropate (**1**).

Reactions of Ethyl Atropate with Primary Amines. A. With Benzylamine.—A solution of 1.4 g (0.008 mol) of ethyl atropate and 0.86 g (0.008 mol) of benzylamine in 5 ml of absolute ethanol was allowed to stand at 25° for 24 hr. Subsequent removal of solvent under reduced pressure gave a thick oil which, upon distillation, afforded 1.6 g (71%) of ethyl 2-phenyl-3-N-benzylamino propanoate (**23a**): bp 172–174° (1 mm); ir (neat) 3350 (NH) and 1725 cm^{-1} (C=O); nmr (CCl_4) δ 7.2 (m, 10, ArH), 4.05 (q, 2, OCH_2), 3.71 (s, 2, $ArCH_2N$), 3.1 (m, 3, CH, CH_2N), 1.45 (s, 1, NH), and 1.10 (t, 3, CH_3).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.19; H, 7.29; N, 4.88.

B. With *n*-Butylamine.—As in part A, 4.4 g (0.025 mol) of ethyl atropate and 1.85 g (0.025 mol) of *n*-butylamine were condensed in 10 ml of absolute ethanol. Work-up gave 3.12 g (50%) of ethyl 2-phenyl-3-*n*-butylaminopropanoate (**23b**): bp 107–108° (0.2 mm); nmr (CCl_4) δ 7.26 (m, 5 ArH), 4.10 (q, 2, OCH_2), 3.15 (m, 5, CH_2, CH), and 1.10 (m, 10, CH_2, CH_3).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.29; N, 5.62. Found: C, 72.45; H, 9.38; N, 5.81.

Miscellaneous Condensations of Diethylamine with Ethyl Atropate. A. In the Absence of Bases.—To 0.9 g (0.012 mol) of diethylamine in 25 ml of absolute ethanol containing a few crystals of hydroquinone was added, in 1-ml portions, a solution of 4.4 g (0.025 mol) of ethyl atropate in 5 ml of absolute ethanol.[18] After 6 days, the ethanol was stripped and the mixture was distilled to only give 3.22 g (73%) of ethyl atropate, bp 104–106° (3 mm). The nmr of the recovered ester was identical with that of an authentic sample.

B. By Means of Catalytic Quantities of Sodium Alkoxides.—Sodium ethoxide (0.0017 mol) was prepared from 0.04 g (0.0017 g-atom) of sodium in 10 ml of absolute ethanol. The ethanol was removed under high vacuum, and the resulting white solid was treated with a mixture of 1.3 g (0.017 mol) of diethylamine and 2.2 g (0.012 mol) of ethyl atropate. After 30 min, the resulting yellow solution was hydrolyzed by 150 ml of water. The usual work-up and distillation afforded small amounts of volatile products, the nmr of which indicated the presence of only trace amounts of amino ester **18a**. Similar results were obtained when catalytic amounts of commercial sodium methoxide or *n*-butyllithium were employed to affect the condensation.

Likewise, condensation of N-methylaniline with ethyl atropate effected by means of a catalytic amount of sodium ethoxide afforded only trace amounts of the desired amino ester **10c**.

Additions of Diethyl Malonate to Ethyl Atropate.—Solid sodium ethoxide (0.0017 mol), prepared as described above, was treated with a mixture of 2.2 g (0.012 mol) of ethyl atropate and 2.0 g (0.012 mol) of diethyl malonate. The resulting yellow solution was stirred for 30 min and poured into 150 ml of water. After work-up,[15] the resulting crude product was distilled to give 2.3 g (55%) of 1-phenyl-1,3,3-tricarbethoxypropane (**24**): bp 185–187° (1.5 mm) [lit.[8] bp 215° (15 mm)]; nmr ($CDCl_3$) δ 7.1 (s, 5, ArH), 4.0 (m, 6, OCH_2), 3.3 (m, 2, CH), 2.4 (q, 2, CH_2), and 1.1 (m, 9, CH_3).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 24.28; H, 7.14. Found: C, 64.48; H, 7.17.

When the reaction was repeated using 4.4 g (0.025 mol) of ethyl atropate, 4.0 g (0.025 mol) of diethyl malonate, and 0.19 g (0.0035 mol) of commercial sodium methoxide, ester **24** was obtained in 60% yield.

When the reaction was repeated using 1 equiv of sodium ethoxide in 100 ml of absolute ethanol for 5 hr, 0.4 g (5%) of ester **24** was obtained, bp 185–187° (1.5 mm). Much polymeric material remained in the pot.

Likewise, when the reaction was effected by 1 equiv of sodium amide in ammonia for 5 min, 1.98 g (24%) of ester **24** was obtained; ethyl atropate and diethyl malonate were recovered in yields of 21 and 50%, respectively.

β Elimination of Ethyl 2-Phenyl-3-N-methylanilinopropanoate (18c).—To a solution of 50 ml of absolute ethanol containing a catalytic amount of sodium ethoxide was added 2.83 g (0.01 mol) of ester **18c** and the yellow solution was refluxed for 24 hr. The solution was cooled to room temperature and treated with several drops of acetic acid, and the solvent was removed to afford an oily residue. Subsequent distillation gave 0.3 g (29%) of methylaniline (identified by comparison of its ir spectrum and boiling point with those of an authentic sample), 0.1 g of recovered amino ester **18c**, bp 174–178° (1.2 mm), a small amount of ethyl atropate, bp 70–75° (1 mm), and about 1.5 g of polymeric material.

Registry No.—**1,** 22286-82-4; **6,** 22286-83-5; **9,** 22286-84-6; **10,** 22286-85-7; **13,** 2286-86-8; **15,** 22319-44-4; **18a,** 22286-87-9; **18b,** 22319-45-5; **18c,** 22286-88-0; **21a,** 22319-46-6; **21b,** 22286-89-1; **22,** 22319-47-7; **23a,** 22319-48-8; **23b,** 22286-90-4; **24,** 22319-49-9.

(18) This procedure is similar to that described for the condensation of methylamine with ethyl acrylate (ref 12).