47%), m.p. 214–228°, of *trans*-cyclohexane-1,2-dicarboxylic acid. The viscous red filtrate was estimated by integration of the vapor phase chromatography trace to be 90% 3,4,5,6-tetrahydrothiophthalide (179 g., 1.16 moles, 47%). The benzene wash solution was added to the viscous red oil and the resulting solution extracted with 5% aqueous sodium bicarbonate. The benzene was then evaporated and the oil cooled to 0°. The oil partially crystallized, and a sticky yellow solid was collected. Two recrystallizations of the yellow solid from methanol (with charcoal) gave 3,4,5,6-tetrahydrothiophthalide as white crystals (74 g., 0.48 mole, 19%), m.p. 36–43°. Further recrystallizations gave white crystals, m.p. 42–43°; λ_{max} in 95% ethanol: 233 mμ (log ϵ 4.02), 258 inflection (3.43); $\nu_{C=O}$ 1690, $\nu_{C=C}$ 1655 cm.$^{-1}$ in carbon tetrachloride. The nuclear magnetic resonance spectrum[18] showed the following absorptions (in τ-values, tetramethylsilane external standard): 8.25, quartet, unconjugated methylene; 7.70, diffuse multiplet, vinyl methylene; 6.17, singlet, split slightly, vinyl methylene adjacent to sulfur; calculated area ratio 2:2:1; observed, 2.1:2.1:1.

Anal. Calcd. for $C_8H_{10}OS$ (154.31): C, 62.26; H, 6.53; S, 20.68. Found: C, 61.98; H, 6.48; S, 20.52. The molecular weight as determined by mass spectrometry was 154.

When this reaction was repeated in a freshly reamed autoclave, the product oil after separation of the solid diacid, was estimated to contain 69% 3,4,5,6-tetrahydrothiophthalide and 21% thiophthalide.

(18) The n.m.r. spectrum was obtained on a Varian A-60 spectrometer.

2-Amino-5,6-dihydro-1,3-oxazines. The Reduction of Carboxylic Esters with Sodium Borohydride[1]

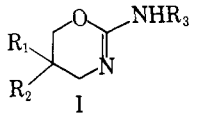
JOSEPH A. MESCHINO AND CAROL H. BOND

McNeil Laboratories, Inc., Fort Washington, Pennsylvania

Received June 21, 1963

Several 5-substituted 2-amino-5,6-dihydro-1,3-oxazines (Table III) were prepared by the cyclization of the appropriately substituted 1,3-amino alcohols (Table II) with cyanogen bromide. The amino alcohols were prepared most readily by a two-step process: (1) sodium borohydride reduction of α-substituted cyanoacetates to the novel hydracrylonitriles (Table I), and (2) lithium aluminum hydride reduction of these to the requisite amino alcohols. A side product of step 1 has been shown to result from the reduction of the nitrile function with sodium borohydride.

The 2-amino-5,6-dihydro-1,3-oxazine system (I) has apparently received little attention. In 1890 Gabriel and Lauer[2] described the parent compound (I, $R_1 = R_2 = R_3 = H$) and more recently Najer and co-workers[3] reported the synthesis of several N-substituted derivatives (I, $R_1 = R_2 = H$; R_3 = alkyl, aryl, and aralkyl). Our interest in this system concerned the possible biological activity of analogs in which the 5-position was substituted (*e.g.*, I, $R_1 = R_2$ = phenyl; $R_3 = H$).

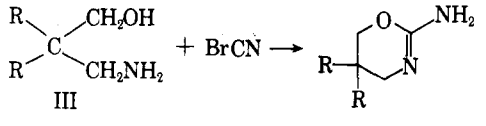


I

$R_3NHCONHCH_2CH_2CH_2Cl$

II

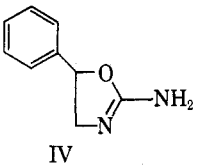
The general method employed by the earlier workers was cyclization of the appropriately N-substituted N′-γ-chloropropylureas (II) in boiling water. Our approach was the cyclization of 2-substituted 1,3-amino alcohols (III) with cyanogen bromide. The



III

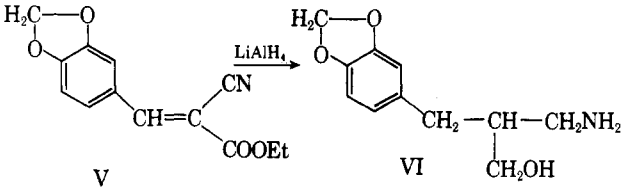
analogous reaction between 1,2-amino alcohols and cyanogen bromide to give the corresponding 2-aminooxazolines (*e.g.*, IV) has been reported.[4]

The requisite 1,3-amino alcohols were in general new compounds. In the search for a method of preparation,



IV

we were attracted by the report[5] that lithium aluminum hydride reduces α,β-unsaturated cyanoacetates (*e.g.*, V) to the corresponding saturated amino alcohols (VI). Numerous attempts to reproduce these results led only to poor yields of colored oils from which none of the desired amino alcohols could be isolated.[6] Two exceptions were noted, namely, ethyl methylphenylcyanoacetate and ethyl diphenylcyanoacetate (see XXXI and XXXII, respectively, Table II). Evidently, disubstitution of the α-position of ethyl cyanoacetate allows reduction with lithium aluminum hydride to proceed satisfactorily.



V VI

The desired amino alcohols were finally obtained by either of the two following methods.

1. Nickel-catalyzed hydrogenation of the α,β-unsaturated cyanoacetates (*e.g.*, V) to give the corresponding amino esters (*e.g.*, VII).[7] The latter sub-

(1) Presented in part at the Fourth Delaware Valley Regional Meeting, Philadelphia, Pa., January 25–26, 1962.

(2) S. Gabriel and S. Lauer, *Ber.*, **23**, 95 (1890).

(3) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 611 (1959).

(4) G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952); R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961); G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszowski, N. M. Kelley, and J. McGowan, *J. Med. Chem.*, **6**, 266 (1963).

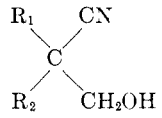
(5) A. Dornow, G. Messwarb, and H. H. Frey, *Ber.*, **83**, 445 (1950).

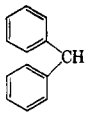
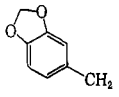
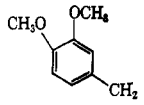
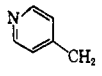
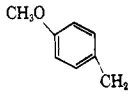
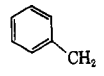
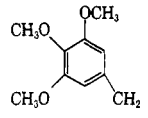
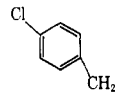
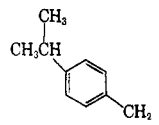
(6) The extraordinary work-up and isolation techniques employed by Dornow, *et al.*, and the generally poor yields reported suggest that they experienced similar difficulties.

(7) R. R. Burtner and J. W. Cusie, *J. Am. Chem. Soc.*, **65**, 262 (1943), used a similar method to reduce methyl diphenylcyanoacetate to the amino ester.

TABLE I

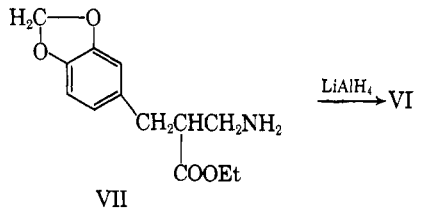
HYDRACRYLONITRILES



Compound no.	R_1	R_2	M.p. or b.p. (mm.), °C.	Recrystd. from	Yield, %	Formula	Calcd.	Found
XII		H	104–105	Ether–pet. ether	80	$C_{16}H_{15}NO$	C 80.98 H 6.37 N 5.90	C 80.85 H 6.45 N 5.65
VIII		H	153 (0.5)		96	$C_{11}H_{11}NO_3$	N 6.83	N 6.62
XXII		H	95.5–96.5	EtOH	91	$C_{12}H_{15}NO_3$	C 65.14 H 6.83 N 6.33	C 65.02 H 6.82 N 6.12
XXIII		H	68–69	$CHCl_3$–ether	68	$C_9H_{10}N_2O$	C 66.65 H 6.22	C 66.81 H 6.46
XXIV		H	43.5–44.5 135° (0.1)		90	$C_{11}H_{13}NO_2$	C 69.09 H 6.85	C 69.30 H 6.80
XXV		H	90 (0.1)		50	$C_{10}H_{11}NO$	C 74.51 H 6.88 N 8.69	C 74.28 H 7.12 N 8.96
XXVI		H	65–66	EtOH	94	$C_{13}H_{17}NO_4$	C 62.14 H 6.82 N 5.57	C 62.41 H 7.08 N 5.40
XXVII		H	138–48 (0.1)		50	$C_{10}H_{10}ClNO$	N 7.16	N 6.77
XXVIII		H	140–142 (0.1)		81	$C_{13}H_{17}NO$	N 6.89	N 6.74
XIV	C_6H_5	C_6H_5	65–66	Ether–pet. ether	85[a]	$C_{15}H_{13}NO$	C 80.69 H 5.87 N 6.27	C 80.58 H 6.08 N 6.18

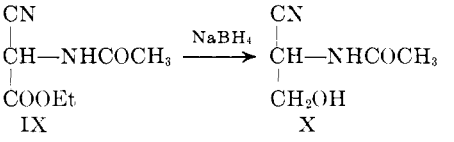
[a] Prepared from diphenylacetonitrile and formaldehyde (see Experimental).

stances were readily converted to the amino alcohols (*e.g.*, VI) with lithium aluminum hydride with none of the previously described difficulties.

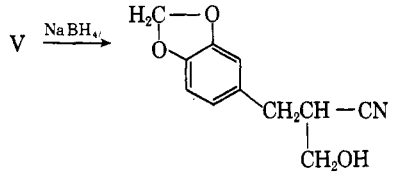


VII

2. Chemical reduction of the α,β-unsaturated cyanoacetates with sodium borohydride to the corresponding saturated hydracrylonitriles (*e.g.*, VIII). A related reduction, namely, that of ethyl α-acetamidocyanoacetate (IX) to α-acetamidohydracrylonitrile (X) with sodium borohydride, has been reported.[8] The hydracrylonitriles (VIII) were then reduced to the desired amino alcohols with lithium aluminum hydride.

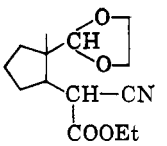


IX X



VIII

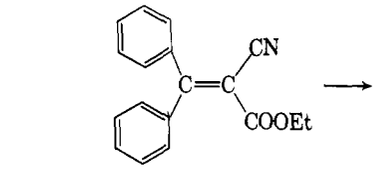
(8) L. Berlinguet, *Can. J. Chem.*, **33**, 1119 (1955); G. W. K. Cavill and F. B. Whitfield, *Proc. Chem. Soc.*, 380 (1962), report the sodium borohydride reduction of i to the corresponding cyano-alcohol. No experimental details are given. We thank Dr. Richard K. Hill of Princeton University for bringing this report to our attention.



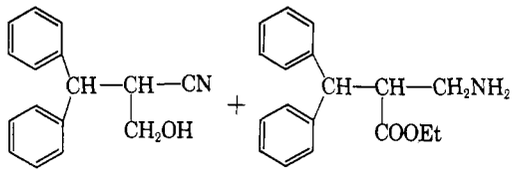
i

While method 1 afforded adequate yields of amino alcohols for subsequent cyclization, method 2 was used almost exclusively when it became clear that in terms of yields and simplicity of operation it was the more satisfactory.

A basic by-product in the reduction of ethyl α-cyano-β-phenylcinnamate (XI) with sodium borohydride in diglyme was identified as ethyl α-diphenylmethyl-β-alaninate (XIII), isolated in 8% yield. This product was identical with that obtained by catalytic



XI



XII 80 %

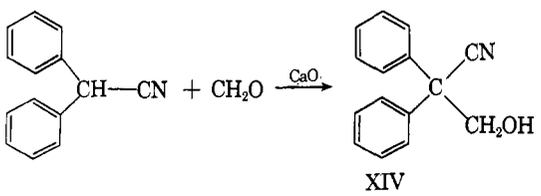
XIII 8 %

(nickel) hydrogenation of XI. Apparently, this is the first reported instance of the reduction of a nitrile with sodium borohydride. It is interesting to note that with isopropyl alcohol (the usual solvent for these reductions), a negligible amount of basic product was obtained. The scope of this side reduction has yet to be studied.

The hydracrylonitriles (Table I) were found to be surprisingly stable to heat; *e.g.*, several of them were purified by distillation at temperatures around 150°; they form the usual derivatives, *e.g.*, tosylates, urethans, carbamates. They are readily hydrolyzed with alkaline peroxide to the corresponding hydracrylamides and with thionyl chloride they are converted to the corresponding β-chloropropionitriles.

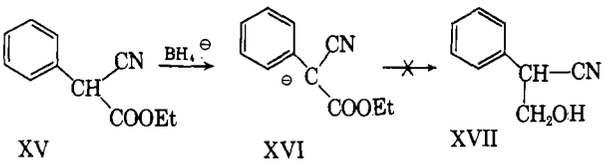
Two cases that follow are worthy of further note.

1. While ethyl diphenylcyanoacetate is converted to diphenylhydracrylonitrile (XIV) with sodium borohydride, the yield is poor (*ca.* 40%). A better method for preparing XIV is condensation of diphenylacetonitrile with formaldehyde in the presence of a base such as calcium oxide.



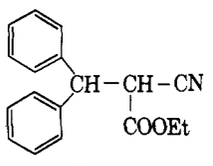
XIV

2. Ethyl phenylcyanoacetate (XV) was recovered unchanged when treated with sodium borohydride. The vigorous evolution of gas when the reagents are brought together suggests the formation of anion XVI which is apparently resistant to further attack by BH_4^-.[9] Wheeler and Wheeler[10] report that carboxylate ion may likewise inhibit attack of BH_4^- at another center of the molecule.



XV XVI XVII

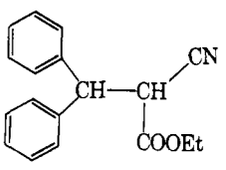
Conversions of carboxylic esters to the corresponding primary alcohols with sodium borohydride are not generally observed[11] although exceptions have been noted.[12] That the α,β-unsaturation has little to do with the reduction of the ester function is evident from the fact that both ethyl diphenylcyanoacetate and ethyl α-cyano-β-phenylhydrocinnamate (XVIII)[13] are reduced to the respective hydracrylonitriles with sodium borohydride and it is likely that the first step in the reduction of α,β-unsaturated cyanoacetates is attack of hydride ion at the β-position.[14] Since several diethyl malonates studied in this laboratory were found to



XVIII

be totally resistant to the action of sodium borohydride, one must conclude that the strongly electron-withdrawing nitrile function plays a major role in the facile reductions observed here, probably by enhancing the electrophilic character of the carbethoxy function (see XIX).

(9) Ethyl α-cyano-β-phenylhydrocinnamate (ii), while possessing an α-hydrogen, is reduced to the corresponding hydracrylonitrile (XII) with sodium borohydride. This would indicate that an α-phenyl group such as that present in XV makes the α-hydrogen appreciably more acidic towards sodium borohydride.



ii

(10) D. M. S. Wheeler and M. M. Wheeler, *J. Org. Chem.*, **27**, 3796 (1962).

(11) S. W. Chaikin and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949). For reductions in the presence of aluminum chloride, boron trichloride, and lithium iodide, see H. C. Brown and B. C. Subba Rao, *ibid.*, **77**, 3164 (1955); H. C. Brown, U. S. Patent 2,945,886; R. Paul and N. Joseph, *Bull. soc. chim. France*, 550 (1952), respectively. Presumably, these additives do not enhance the reductive powers of sodium borohydride but convert it, *in situ*, to a more reactive hydride. For example, the addition of lithium halide produces lithium borohydride [H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.* **77**, 6209 (1955)], a reagent which readily reduces esters [R. F. Nystrom, S. W. Chaikin, and W. G. Brown, *ibid.*, **71**, 3245 (1949)].

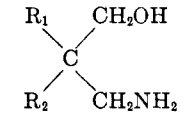
(12) See N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 503. The examples include two steroidal methyl esters and several methyl uronates. See also, J. Kollonitsch, O. Fuchs, and V. Gabor, *Nature*, **175**, 346 (1955). These authors give no examples or experimental details.

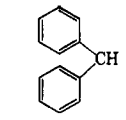
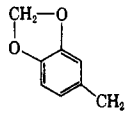
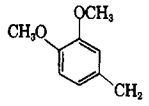
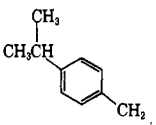
(13) E. P. Kohler and M. Reimer, *Am. Chem. J.*, **33**, 333 (1905).

(14) H. Le Moal, R. Carrié, and M. Bergain, *Compt. rend.*, **251**, 2541 (1960), report that potassium borohydride in methanol reduces ethyl α-cyano-β-phenylcinnamate (XI) to the dihydro compound, *i.e.*, XVIII.

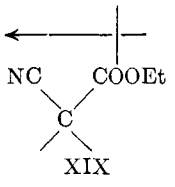
TABLE II

3-AMINO-1-PROPANOLS

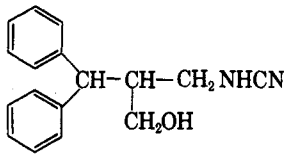


Compound no.	R_1	R_2	M.p., °C.	Recrystd. from	Yield, %	Formula	Calcd.	Found
XXIX		H	157–159[a]	EtOH–ether	87[b] 86[e]	$(C_{16}H_{19}NO)_2C_4H_4O_4$[c]	N 4.68	N 4.39
VI		H	173–174[d]	MeOH	40	$(C_{11}H_{15}NO_3)_2C_4H_4O_4$	N 5.24	N 5.14
XXX		H	162–163	MeOH	40	$C_{12}H_{19}NO_3 \cdot C_4H_4O_4$	N 4.10	N 4.35
XXXI	C_6H_5	CH_3	114 subl.	MeOH	42[f]	$C_{10}H_{15}NO \cdot C_4H_4O_4$	C 59.77 H 6.81 N 4.98	C 59.93 H 7.00 N 4.86
XXXII	C_6H_5	C_6H_5	176–177[g]	Aqueous EtOH	71[h]	$C_{15}H_{17}NO \cdot C_4H_4O_4$	N 4.08	N 4.30
XXXIII		H	152 then 171–172	MeOH–ether	43	$C_{13}H_{21}NO \cdot HCl$	N 6.76	N 6.65

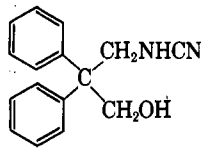
[a] The free base melts 99.5–104.5°. [b] Using ethyl α-diphenylmethyl-β-alaninate as starting material, the yield was 77%. [c] $C_4H_4O_4$ refers to fumaric acid. [d] Dornow, *et al.*, ref. 4, report m.p. 140° for the oxalate salt. [e] Using ethyl α-(3,4-methylenedioxybenzyl) alanine as starting material, the yield was 40%. [f] Ethyl methylphenylcyanoacetate was starting material. [g] The free base melts 108–108.5°. [h] Using ethyl diphenylcyanoacetate as starting material, the yield was 47%.



XIX



XX

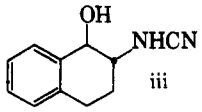


XXI

Reduction of the acrylonitriles with lithium aluminum hydride afforded the requisite, 1,3-amino alcohols in good yields (Table II). These subsequently reacted with cyanogen bromide to give the desired 2-amino-1,3-oxazines in moderate yields (Table III). In most cases, the intermediate cyanamide alcohol could be isolated and in one case (XX) it was characterized. This behavior contrasts sharply with that observed in the case of 1,2-amino alcohols,[4] where the intermediate cyanamide alcohols cyclize spontaneously in every reported case.[15]

Cylization of the intermediate cyanamide alcohols was found to occur readily upon treatment with anhydrous hydrogen chloride. In one case (XXI), however, cyclization took place spontaneously, a probable consequence of the two phenyl groups forcing the cyanamide and alcohol functions closer together.

(15) A private communication from G. I. Poos, and J. D. Rosenau of these laboratories, reveals that at least one exception to this has been found, namely, iii, which is obtained from the corresponding amino alcohol upon treatment with cyanogen bromide. The details of this and other related work will appear elsewhere.



iii

Experimental

All melting points are uncorrected and were taken on a Thomas–Hoover capillary melting point apparatus.

The starting α,β-unsaturated cyanoacetates were prepared from the appropriate aldehydes and ethyl cyanoacetate by known methods.[16] Ethyl diphenylcyanoacetate was prepared from ethyl chlorodiphenylacetate and mercurous cyanide.[17] Ethyl methylphenylcyanoacetate was prepared by methylating ethyl phenylcyanoacetate.[18]

The descriptions which follow are general methods and applicable to all examples in Table I–III unless otherwise noted.

Hydracrylonitriles (Table I). Method A.—To a stirred, cooled (15°) solution of 3.6 g. (0.1 mole) of sodium borohydride in 50 ml. of diglyme was added over a period of 15 min. a solution of 10 g. (0.036 mole) of ethyl α-cyano-β-phenylcinnamate in 50 ml. of diglyme. The temperature was allowed to reach room temperature and stirring maintained for 3 hr. after which the mixture was poured over water and extracted with ether several times. The combined organic solutions were washed twice with 2 *N* HCl and finally once with water. After drying over anhydrous sodium sulfate and concentration *in vacuo* there remained 7.5 g. of a crystalline residue, m.p. 90–100°, which was recrystallized from ether–petroleum ether to give 6.8 g. (80%) of analytically pure α-diphenylmethylhydracrylonitrile, m.p. 104–105°;

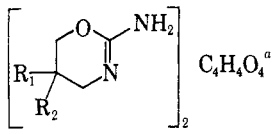
(16) E. J. Cragoe, Jr., C. M. Robb, and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950); F. D. Popp, *ibid.*, **25**, 646 (1960).

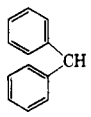
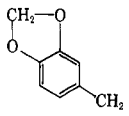
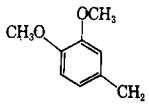
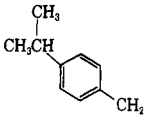
(17) A. Bickel, *Ber.*, **22**, 1537 (1889).

(18) S. Wideqvist, *Chem. Zentr. II*, 1184 (1943).

TABLE III

2-AMINO-5,6-DIHYDRO-1,3-OXAZINES



Compound no.	R_1	R	M.p., °C.	Recrystd. from	Yield, %	Formula	Calcd.	Found
XXXIV		H	209–211	*b*	65	$(C_{17}H_{18}N_2O)_2C_4H_4O_4$	C 70.35 H 6.22 N 8.64	C 70.29 H 6.43 N 8.53
XXXV		H	178–180	Aqueous EtOH	40	$(C_{12}H_{14}N_2O_3)_2C_4H_4O_4$	C 57.53 H 5.52 N 9.59	C 57.59 H 5.76 N 9.16
XXXVI		H	196.5–197	EtOH	46	$(C_{13}H_{18}N_2O_3)_2C_4H_4O_4$	C 58.43 H 6.54	C 58.55 H 6.58
XXXVII	C_6H_5	CH_3	234 dec.	Aqueous EtOH	50	$(C_{11}H_{14}N_2O)_2C_4H_4O_4$	N 11.28	N 11.04
XXXVIII	C_6H_5	C_6H_5	248 dec.	*b*	65	$(C_{16}H_{16}N_2O)_2C_4H_4O_4$	C 69.66 H 5.85 N 9.03	C 69.66 H 5.85 N 8.68
XXXIX		H	194.5 dec.	MeOH	70	$(C_{14}H_{20}N_2O)_2C_4H_4O_4$	N 9.65	N 9.63

[a] $C_4H_4O_4$ signifies fumaric acid. [b] Purified by boiling in ethanol or 2-propanol.

λ_{max}^{KBr} 2.86, 3.25, 3.35, 3.41, 4.39, 6.22, 6.65, 6.84 μ; λ_{max}^{MeOH} 221, 263 mμ; ϵ 9800, 230. The analytical data are reported in Table I.

The aqueous acidic washes of the reaction mixture were made basic with concentrated sodium hydroxide solution and extracted with ether. The organic solution was worked up in standard fashion to yield 1 g. of oil which was converted to a hydrochloride salt, m.p. 199–201°. The yield was 0.85 g. (8%). Comparison with an authentic sample showed this material to be ethyl α-diphenylmethyl-β-alaninate hydrochloride.

Method B.—To a stirred, cooled (15°) suspension of 11.4 g. (0.3 mole) of sodium borohydride in 50 ml. of 2-propanol was added over 5 min. a solution of ethyl α-cyano-β-phenylcinnamate in 200 ml. of 2-propanol. After stirring for 8 hr., the excess borohydride was destroyed with dilute acetic acid and most of the 2-propanol removed *in vacuo*. From this point, the reaction was worked up as previously described in method A. The yield of α-diphenylmethylhydracrylonitrile was comparable to that obtained from the diglyme system, although the amount of basic material obtained was negligible.

Method C (for α,α-Diphenylhydracrylonitrile Only).—To a stirred mixture of 25 g. (0.13 mole) of diphenylacetonitrile, 11.5 g. (0.38 mole) of paraformaldehyde, 30 ml. of water, and 100 ml. of tetrahydrofuran was added in several portions 5.5 g. (0.1 mole) of calcium oxide. The temperature rose to about 30° after which it returned to room temperature and stirring was continued for 8 hr.

The mixture was then made slightly acidic with formic acid and concentrated to near dryness *in vacuo*. The residue was diluted with water and extracted several times with ether after which the combined ether solutions were washed with water, dried over anhydrous potassium carbonate, and concentrated to dryness leaving about 30 g. of an oil which slowly crystallized. The yield of pure crystalline α,α-diphenylhydracrylonitrile (recrystallized from ether–petroleum ether) was only about 15 g. (52%), although if the crude product is treated with lithium aluminum hydride a 71% yield of the corresponding amino alcohol, *i.e.* 3-amino-2,2-diphenyl-1-propanol is obtained.

α,α-Diphenylhydacrylonitrile has the following physical properties: m.p. 65–66°; λ_{max}^{KBr} 2.88, 3.25, 3.40, 4.44, 6.24, 6.67, 6.88 μ. The analytical data are reported in Table I.

Amino Alcohols (Table II).—To a stirred suspension of 3.9 g. (0.1 mole) of lithium aluminum hydride in 75 ml. of anhydrous ether was added, over a convenient period, a solution of 9 g. (0.03 mole) of α-diphenylmethylhydracrylonitrile (or an equivalent amount of ethyl α-diphenylmethyl-β-alaninate) in 100 ml. of ether. After stirring for 5 hr., the excess hydride was destroyed with water, the ether solution filtered and concentrated to dryness. The residue, 6.5 g., was recrystallized from ether–hexane to give 6.1 g. (79%) of pure 3-amino-2-diphenylmethyl-1-propanol, m.p. 99.5–104.5°; λ_{max}^{KBr} 3.14, 3.40, 3.45, 6.24, 6.65, 6.85 μ.

Where the amino alcohols were oils or difficultly recrystallizable, they were converted to a convenient salt (see Table II) and characterized.

2-Amino-5,6-dihydro-4*H*-1,3-oxazines (Table III).—To a stirred, cooled (10°) mixture of 8 g. (0.03 mole) of 3-amino-2-diphenylmethyl-1-propanol and 5.6 g. (0.06 mole) of sodium acetate in 100 ml. of methanol was added drop by drop a solution of 3.6 g. (0.034 mole) of cyanogen bromide in 50 ml. of methanol. The homogeneous mixture was then stirred for 8 hr.

The solution was concentrated to near dryness and the residue treated with cold concentrated aqueous sodium hydroxide. The mixture was then extracted with ether several times after which the combined ether solutions were washed once with water, dried over anhydrous potassium carbonate, and evaporated to dryness. The crystalline residue was recrystallized from benzene to give 7.4 g. (84%) of 2-diphenylmethyl-3-hydroxypropylcyanamide, m.p. 91–92° (with subsequent resolidification and fusion at 205°); λ_{max}^{KBr} 2.98, 3.19, 3.40, 4.46, 6.23, 6.66, 6.68 μ.

Anal. Calcd. for $C_{17}H_{18}N_2O$: N, 10.52. Found: N, 10.31.

When the previously described substance was dissolved in ether and treated with anhydrous hydrogen chloride, a hygroscopic solid precipitated. From this 5.1 g. of the free amine, m.p. 197–200°, was obtained.[19] This was converted to a fumarate salt, m.p. 209–211°; the yield was 3 g. (31%); λ_{max}^{KBr} 3.04, 3.40, 5.88, 6.50, 6.84 μ. The analytical data are reported in Table III.

Ethyl α-Diphenylmethyl-β-alaninate Hydrochloride.—In a stainless steel autoclave was placed 10 g. (0.036 mole) of ethyl α-cyano-β-phenyl cinnamate, about 10 g. of triethylamine, about 2 g. of sponge nickel catalyst (Davison Chemical Co.), and 150

(19) Whether this was the product obtained upon melting 2-diphenylmethyl-3-hydroxypropylcyanamide (note its melting point) was not investigated.

ml. of absolute ethanol. The autoclave was then shaken under 1,000 lb. of hydrogen pressure at 100° for 1 hr.

After filtration, the solution was concentrated *in vacuo* and the oily residue taken up in ether and separated into basic and neutral fractions. The basic fraction was converted to its hydrochloride salt and recrystallized from ethanol–ether to give 5.8 g. (50%) of analytically pure ethyl α-diphenylmethyl-β-alaninate hydrochloride, m.p. 200–202°; λ_{max}^{KBr} 3.50, 5.80, 6.15, 6.22, 6.29, 6.65, 6.84 μ; λ_{max}^{MeOH} 258 mμ, ε 475.

Anal. Calcd. for $C_{18}H_{21}NO_2 \cdot HCl$: C, 67.59, H, 6.94; N, 4.38. Found: C, 67.89; H, 7.01; N, 4.36.

Acknowledgment.—We wish to thank Dr. George I. Poos who suggested the original problem for helpful discussions, and Mrs. Mary Christie for the spectroscopic data and nitrogen analyses.

Reactions of Acetylenic Esters with Enamines

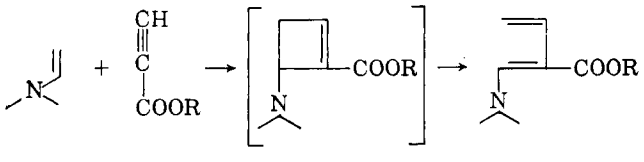
CHARLES F. HUEBNER, L. DORFMAN, MICHAEL M. ROBISON, ELLEN DONOGHUE, WILLIAM G. PIERSON, AND PATRICIA STRACHAN

Research Department, Ciba Pharmaceutical Company, Division of Ciba Corporation, Summit, New Jersey

Received June 10, 1963

Enamines derived from cyclic ketones react with ethyl propiolate or dimethyl acetylenedicarboxylate to produce intermediate cyclobutene adducts which have, in several cases, been isolated. These cyclobutenes on heating, undergo bond rearrangement with expansion of the cyclic ketone ring by two carbon atoms. In at least one case, however, treatment with dilute acid in the cold results in a second reaction course to form a Michael-type adduct of the ester and cyclic ketone. Reactions of dimethyl acetylenedicarboxylate with enamines derived from β-diketones and β-keto esters also are described.

Since the introduction by Stork and co-workers[1] in 1954 of a relatively general procedure for the alkylation of carbonyl compounds *via* their enamine derivatives, reactions of the latter with a wide variety of electrophiles have been studied by various investigators.[1] Although alkylations with electrophilic olefins, reported in 1956[2], have been widely studied,[1] little, until recently, has been known about the corresponding reactions of enamines with electrophilic acetylene compounds. The earliest report of such a reaction, in abstract form,[3] indicates that enamines react with conjugated acetylenic esters to produce an intermediate cyclobutene adduct, which rearranges in such a manner as to interpose the two acetylenic carbon atoms between the erstwhile olefinic carbons of the enamine. We had been independently studying this reaction for



some time with both cyclic and acyclic[4] enamines when we became aware of the activities of two other groups of investigators in this field. Bose and Minah[5] have reported on reactions of enamines of cyclic ketones with dimethyl acetylenedicarboxylate and with methyl propiolate to yield ring-expanded products by an analogous process, and a pending paper by Berchtold[6] is concerned with the dimethyl acetylenedicarboxylate reaction in similar cases. In spite of some duplication in these investigations, we present our findings on reactions of cyclic enamines here, for they include certain unique results, among these the *isolation of several of the intermediate cyclobutene adducts.* In addition we have found that the cyclobutenes may, at least in certain cases, be converted *either* to the ring-expanded derivatives,[5,6] *or* (on hydrolysis) *to the unsaturated keto esters corresponding to Michael-type additions of acetylenic esters to ketones.* In addition, we report here reactions of acetylenic esters with various acyclic enamines derived from β-diketones or β-keto esters, the courses of which are widely diverse in nature.

The early experiments with ethyl propiolate were carried out by addition of the ester to a dioxane solution of 1-pyrrolidinocyclopentene (**1a**) at ambient temperature, and subsequent heating of the mixture on the steam bath. Removal of solvent allowed isolation of the crystalline 1-pyrrolidino-2-carbethoxy-1,3-cycloheptadiene (**3**). The structure of this substance was indicated by infrared bands at 1661 and 1605 cm.$^{-1}$ (Nujol) representing C=O and C=C absorptions, respectively. In the n.m.r. spectrum[7] the C-3 proton was observed as a doublet at 6.45 δ ($J_{3,4}$ = 10.1) and H-4 as a triplet of a doublet at 5.70 δ ($J_{3,4}$ = 10.1, $J_{4,5,5}$ = 6.4). Chemical confirmation of the structure was obtained in several ways. Mild acid hydrolysis of the enamine group resulted in the formation of the keto–enol mixture (**4**), which was reduced catalytically to the known[8] 2-carbethoxycycloheptanone (**6**). This keto ester was identified by its reaction with phenylhydrazine to yield the solid phenylpyrazolone derivative,[8] and by its hydrolysis and decarboxylation to cycloheptanone, the semicarbazone of which was compared with an authentic sample. The sequence of reactions also was carried out in reversed order, partial hydrogenation preceding the mild hydrolysis to yield the same product.

When, on the other hand, ethyl propiolate and **1a** were allowed to react below room temperature and the

(1) *Cf.* G. Stork, A. Brizzolara, H. Landesman, J. Smuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963), for a recent survey.

(2) G. Stork and H. Landesman, *ibid.*, **78**, 5128 (1956).

(3) K. C. Brannock, Abstracts of Papers, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 450.

(4) *Cf.* C. F. Huebner and E. Donoghue, *J. Org. Chem.*, **28**, 1732 (1963).

(5) A. K. Bose and G. L. Minah, Metropolitan Regional Meeting of the American Chemical Society, Newark, N. J., January 28, 1963.

(6) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963). We wish to thank Dr. Berchtold who, through Dr. F. Greene, made a copy of his paper available to us before publication, on submission of the previous manuscript[4] from this laboratory.

(7) Spectra were obtained with the Varian A-60 spectrometer at 60 Mc./sec. using tetramethylsilane as internal reference. Chemical shifts are quoted in field-independent δ-units (p.p.m.) where δ is defined by the relationship $\delta = 10^6|H_{ref} - H|/H_{ref}$; coupling constants ($J$) are expressed in c.p.s.

(8) W. Dieckmann, *Ber.*, **55** 2485 (1922).