Raney Nickel Catalyst.—The catalyst was prepared in 5- to 15-g lots using the procedure given in "Organic Syntheses"[8] with the following modifications. Addition of nickel–aluminum alloy (50:50) (BHD) to the sodium hydroxide solution was conducted at room temperature (25–30°) and was completed within 20 min, during which time the temperature rose to 90°. Stirring was continued for another 10 min, and the reaction continued directly at steam bath temperature for another 1–2 hr, when evolution of hydrogen stopped. Catalyst thus obtained could be used for three successive runs without appreciable loss in activity.

Acylamino Acid Amides.—Azlactone[9] either in solution or in the form of a suspension (0.025 mol) in ethanol (95%) and ammonia (0.5 mol) catalyst (3 g) was hydrogenated in a Parr hydrogenation apparatus at 32–55 psi for 1–16 hr. Completion of hydrogenation could be read off the gauge provided with the hydrogenation flask and was further marked in most cases either by change in color (*e.g.*, colored to colorless) or by the formation of a flocculent white precipitate. In case of precipitation, which occurred with benzoylphenylalanine amide, benzoyl-3,4-dimethoxyphenylalanine amide, benzoyl-*O*-methyltyrosine amide, benzoyltyrosine amide, and benzoyl-3-methoxy-4-hydroxyphenylalanine amide, the contents were heated to dissolve the amide before filtration of the catalyst. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue thus obtained was crystallized from ethanol (95%).

Reduction of the azlactones of aliphatic aldehydes and ketones generally required less time (1–9 hr) than that of the aromatic ones. Most amides were purified by recrystallization from ethanol (95%), and some aliphatic amides were crystallized from aqueous ethanol (30–80%) (Table I).

***N*-Benzoylamino Acid.**—The above benzoylamino acid amides were converted into the corresponding *N*-benzoylamino acids by heating on a boiling water bath or a sand bath with hydrochloric acid (36%) till complete dissolution occurred. The required benzoylamino acid crystallized out on keeping the reaction mixture overnight. A single recrystallization from ethanol gave an analytically pure sample (Table II).

Amino Acid.—Amino acids were obtained directly from *N*-benzoylamino acid amides by heating them at reflux temperature with hydrochloric acid (36%) for different lengths of time (1.5–6 hr). The amino acid hydrochlorides so obtained were treated with silver oxide, which made isolation of the free amino acids smooth and quantitative (Table III).

Acknowledgment.—We are indebted to Dr. S. M. F. Rahman, Head of the Department, for providing research facilities. One of us (A. B.) is thankful to the University Grants Commission, New Delhi, India, for financial aid.

(8) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).
(9) R. Adams, "Organic Reactions," Vol. III, Wiley, New York, N. Y., 1947, pp 198–239.

C-3 Nucleophilic Substitution of 3-Azetidinyl Tosylates. Alkylation

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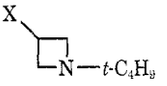
Recently several new 1-*tert*-butylazetidines have been prepared from 1-*tert*-butylazetidines possessing a replaceable functional group at the 3 position. Ohta, *et al.*, reported that 1-*tert*-butyl-3-azetidinyl tosylate reacts with amines and mercaptides to yield 3-aminoazetidines and 3-azetidinyl thioethers, respectively.[2] Gaertner[3] reported that chloroazetidine **2** gives the same results on reaction with these reagents and reacts with alcoholic solutions of alkali metal alkoxides to yield 1-*tert*-butyl-3-alkoxyazetidines. To date, however, the only reported C–C bond forming reaction at C-3 involves the reaction of **1**[2,4] or **2**[3] with cyanide yielding cyanoazetidine **3**. The rate of the reaction



1, X = OTs
2, X = Cl
3, X = CN

of **1** with potassium cyanide in methanol has been shown to be independent of cyanide concentration,[4] which, along with the solvolysis rate data for **1**[4] and the observation that *cis*- and *trans*-1-*tert*-butyl-2-methyl-3-azetidinyl tosylates undergo hydrolysis with stereospecific retention of configuration,[5] seems indicative of an intermediate 1-azabicyclo[1.1.0]butonium ion in the reaction with cyanide and in the solvolysis reactions[4–6] of azetidinyl tosylates.

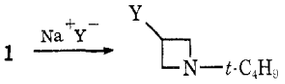
As a continuation of our investigations into the chemistry of functionally substituted azetidines, we have allowed **1** to react with the sodio derivatives of several active methylene compounds. It can be seen from the data in Table I that when the reaction proceeds

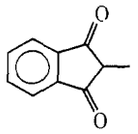
TABLE I
PER CENT YIELDS OF ALKYLATED AZETIDINES OBTAINED FROM THE REACTION OF 1 WITH SODIO DERIVATIVES OF ACTIVE METHYLENE COMPOUNDS

Compd	Solvent	% Alkylation[a]	Solvent	% Alkylation
4	MeOH	0.0	Et_2O	0.0
5	EtOH	11		
6	EtOH	39	Et_2O[b]	~0[c]
7	EtOH	67	Et_2O[b]	8–9[c]

[a] Isolated yield. [b] Contains 1 equiv of ethanol. [c] Per cent of crude azetidinyl product by pmr.

in alcoholic solvent, the yield of alkylated product is significantly better than when the reaction is conducted in ether solvent. Since the reactions in the different solvents were conducted for essentially the same period of time, it may be surmised that the reactions in ether





4, Y =

5, Y = $CN(CO_2Et)CH$
6, Y = $(CO_2Et)_2CH$
7, Y = $Ac(CO_2Et)CH$

(1) To whom correspondence should be addressed.
(2) T.-Y. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **41**, 712 (1968).
(3) V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).
(4) R. H. Higgins, F. M. Behlen, D. F. Eggli, J. H. Kreymborg, and N. H. Cromwell, *ibid.*, **37**, 524 (1972).
(5) R. H. Higgins and N. H. Cromwell, in press.
(6) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).

are considerably less rapid than those in the alcoholic solvent. This is consistent with a cationic intermediate and appears to be inconsistent with the direct displacement mechanism.[7]

The ir and pmr spectra of **5** and **6** are consistent with the expected structures for these compounds. Thus the pmr spectrum of **6** consists of a four-proton quartet[8] centered at δ 4.20 ppm (methylene protons of ethyl groups), a six-proton multiplet at δ 2.90–3.75 (ring protons plus the methine proton of the malonate group) which integrates to five protons upon addition of deuterium oxide, a six-proton triplet[8] at δ 1.28 (methyl protons of the ethyl groups), and a nine-proton singlet[8] at δ 0.93 (*tert*-butyl protons); the infrared spectrum of **6** contains a typical ester carbonyl stretching frequency at 1740 cm^{-1} in carbon tetrachloride. The spectra of **5** are very similar. The pmr spectrum consists of a two-proton quartet at δ 4.26 (methylene protons of the ethyl group), a one-proton doublet (J = 7.4 Hz) at δ 3.77 (methine proton of cyanoacetate group) which disappears on addition of deuterium oxide, a five-proton multiplet at δ 2.67–3.63 (ring protons), a three-proton triplet at δ 1.32 (methyl protons of ethyl group), and a nine-proton singlet at δ 0.95 (*tert*-butyl protons); the infrared spectrum of **5** contains a typical ester carbonyl stretching frequency at 1742 cm^{-1} in deuteriochloroform.

The spectra of **7** are significantly different from those of **5** and **6**. The infrared spectrum (ν_{CCl_4} 3300, 1690, and 1635 cm^{-1}) suggests that the acetoacetate is extensively enolized, a result which was not anticipated since α-alkyl substituents generally decrease the amount of enol present.[9] Additional support for an enol structure for **7** can be obtained from the pmr spectrum: a four-proton multiplet (of which the quartet of the methylene protons of the ethyl group can be observed at δ 4.20) at δ 4.00–4.52 (one set of the C-2,4 protons of the ring and the methylene protons of the ethyl group), a three-proton multiplet at δ 2.27–3.50 (remainder of the ring protons), a three-proton absorption of two singlets[10] centered at δ 2.18 (acetyl protons), a three-proton triplet at δ 1.29 (methyl protons of the ethyl group), a nine-proton absorption of two singlets at δ 1.05 and 0.98 (*tert*-butyl protons) in a ratio of *ca.* 9:1, respectively, and a broad one-proton absorption at δ 0.86 (OH) which disappears on addition of deuterium oxide.

While it is possible that the magnetic nonequivalence of the acetyl and *tert*-butyl protons is the result of the same type of phenomenon observed in the spectrum of **6** (*vide supra*), we are of the opinion that the nonequivalence of these protons in **7** is best described in terms of different enolic structures.[11] The broad absorption at 3300 cm^{-1} seems indicative of predominantly *intermolecular* hydrogen bonding, as upon dilution this absorption is found to have obscured two weaker absorptions at 2285 and 2335 cm^{-1}. Consequently, we suggest that the singlet at δ 1.05 in the pmr spectrum of **7** is due to the *tert*-butyl protons of the intermolecularly hydrogen bonded species, and the singlet at δ 0.98 is due to one (or both) of the intramolecularly hydrogen bonded forms of **7**.

These interesting new derivatives of azetidine are potential starting points in the synthesis of a variety of other azetidines. Such possibilities are being investigated in this laboratory.

(7) See, for example, K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, pp 388–389.

(8) Each member of this absorption appears as two slightly separated ($\Delta\nu$ = 1–2 Hz) absorptions.

(9) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1956, p 446.

(10) Appears as two slightly separated singlets ($\Delta\nu$ = 1 Hz).

(11) We have insufficient data to assign geometrical isomers to any enol other than the chelated one.

Experimental Section[12]

1-*tert*-Butyl-3-azetidinyl Tosylate (1). This compound, which was first prepared by Ohta, *et al.*,[13] was prepared *via* the sodium hydride method.[14]

Preparation of Alkylated Azetidines in Alcoholic Solvent. Attempted Preparation of 2-(1-*tert*-Butyl-3-azetidinyl)indane-1,3-dione (4).—To a solution of 0.525 g (9.73 mmol) of sodium methoxide and 1.42 g (9.72 mmol) of indane-1,3-dione in 100 ml of ether was added 2.75 g (9.72 mmol) of **1**. The solution was stirred for 2 days at room temperature and then evaporated to a viscous yellow-brown oil. Aqueous, saturated sodium carbonate (150 ml) was added, and the solution was extracted twice with equal volumes of ether. The combined ethereal extracts were dried (sodium carbonate). The pmr spectrum of the residue remaining after evaporation of the ether was superimposable on that of 1-*tert*-butyl-3-methoxyazetidine.[4]

Ethyl (1-*tert*-Butyl-3-azetidinyl)cyanoacetate (5).—To 100 ml of an ethanolic solution of sodium ethoxide prepared from 0.60 g (0.025 g-atom) of sodium was added 2.83 g (0.0250 mol) of ethyl cyanoacetate. After stirring for a few minutes, 7.00 g (0.0248 mol) of **1** was added and the solution was stirred for 20 hr (allowing a longer reaction time gave no increase in yield). After filtering, the ethanol was removed *in vacuo*. The filtered salts were washed with ether, the filtrate being added to the residue from evaporation of the ethanol. The ethereal solution was again filtered, and the ether was removed *in vacuo*. Distillation, bp 108–114° (0.8 Torr), afforded 0.61 g (11%) of **5** as a colorless oil which rapidly turned red and resinified on standing.

We were unable to obtain the picrate of **5** in pure form.

Anal. Calcd for $C_{18}H_{23}N_5O_9$ (picrate, mp 180° dec): C, 47.68; H, 5.11; N, 15.50. Found: C, 46.88; H, 5.05; N, 15.98.

Ethyl (1-*tert*-Butyl-3-azetidinyl)acetoacetate (7).—To a solution prepared from 0.60 g (0.025 g-atom) of sodium and 100 ml of ethanol was added 3.35 g (0.025 mol) of ethyl acetoacetate and then 7.00 g (0.0248 mole) of **1**. The solution was stirred at room temperature for 40 hr and then filtered to remove much of the precipitated sodium *p*-toluenesulfonate. The ethanol was removed *in vacuo*. The filtered salt was washed with ether, which was then added to the oily residue obtained after the evaporation of the ethanol; the dry sodium *p*-toluenesulfonate weighed 4.80 g (99%). The ethereal solution of **7** was again filtered, and the ether was removed *in vacuo*. Distillation afforded 4.00 g (67%) of **7** as a nearly colorless liquid, bp 90–95° (0.5 Torr).

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81; mol wt, 241. Found: C, 64.63; H, 9.56; N, 5.72; mol wt, 241 (mass spectrometer).

Diethyl (1-*tert*-Butyl-3-azetidinyl)malonate (6).—To a solution prepared from 0.60 g (0.025 g-atom) of sodium and 100 ml of ethanol was added 4.00 g (0.025 mol) of ethyl malonate and then 7.00 g (0.0248 mol) of **1**. The solution was stirred at room temperature for 64 hr and worked up exactly as described for the preparation of **7**. Distillation, bp 100–104° (0.6 Torr), afforded 2.60 g (39%) of **6** as a colorless liquid. Much resinous material remained in the distilling flask.

(12) Melting points are uncorrected. Microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill., or by Alfred Bernhardt Mikroanalytisches Laboratorium, Hohenweg, West Germany. Pmr spectra were determined on either a Varian A-60 or a Varian A-60D spectrometer in deuteriochloroform solutions containing *ca.* 1% TMS, internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer.

(13) T.-Y. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **40**, 2401 (1967).

(14) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 1063 (1971).

In a subsequent preparation, dry hydrogen chloride gas was passed through the ethereal solution of **6** and ethyl malonate. The ethereal solution of ethyl malonate was carefully decanted from the oily hydrochloride of **6**. The hydrochloride was washed with ether and then liberated to the free amine by the action of an excess of triethylamine in ether. The ethereal solution was then filtered and distilled as before. Compound **6** was again obtained in a 39% yield with slightly less resinification in the distilling flask.

Anal. (picrate, mp 85–86.5°). Calcd for $C_{20}H_{28}N_4O_{11}$: C, 48.00; H, 5.64; N, 11.20. Found: C, 47.86; H, 5.46; N, 11.40.

Attempted Preparation of Alkylated Azetidines in Ether. Attempted Preparation of 2-(1-*tert*-Butyl-3-azetidinyl)indane-1,3-dione (4).—To a solution of 0.52 g (3.56 mmol) of indane-1,3-dione and 0.085 g (3.54 mmol) of sodium hydride in 25 ml of ether, which had been stirred for 15 min, was added 1.00 g (3.53 mmol) of **1**. The mixture was stirred for 30 hr. Water was added, and the ethereal layer was separated and dried (magnesium sulfate). Evaporation of the ether yielded 0.95 g of white solid identified as **1** by pmr spectroscopy.

Attempted Preparation of Diethyl (1-*tert*-Butyl-3-azetidinyl)-malonate (6).—To a solution of sodium ethoxide prepared from 0.57 g (0.0248 g-atom) of sodium and 1.14 g (0.0248 mol) of ethanol in 100 ml of ether was added 4.00 g (0.025 mol) of ethyl malonate. After *ca.* 20 min 7.00 g (0.025 mol) of **1** was added. After 48 hr the mixture was filtered and the ether was removed *in vacuo*. The pmr spectrum of the crude product indicated little if any **6**.

Preparation of Ethyl (1-*tert*-Butyl-3-azetidinyl)acetoacetate (7).—To a solution of sodium ethoxide prepared from 0.57 g (0.0248 g-atom) of sodium and 1.14 g (0.0248 mol) of ethanol in 100 ml of ether was added 3.35 g (0.025 mol) of ethyl acetoacetate. After stirring for *ca.* 20 min, 7.00 g (0.025 mol) of **1** was added. After stirring for 48 hr the mixture was filtered, and the ether was removed from the filtrate *in vacuo*. The pmr spectrum indicated 8–9% of the azetidine to be **7**, the remainder unreacted **1**.

Registry No.—**1**, 17358-65-5; **5**, 34910-31-1; **5** picrate, 34910-32-2; **6**, 34910-33-3; **6** picrate, 34910-34-4; **7**, 34910-35-5.

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A Solvolytic Fission of a Carbon–Fluorine Bond Induced by Triethyl Orthoformate in 6β-Fluoro-17α-acetoxyprogesterone[1]

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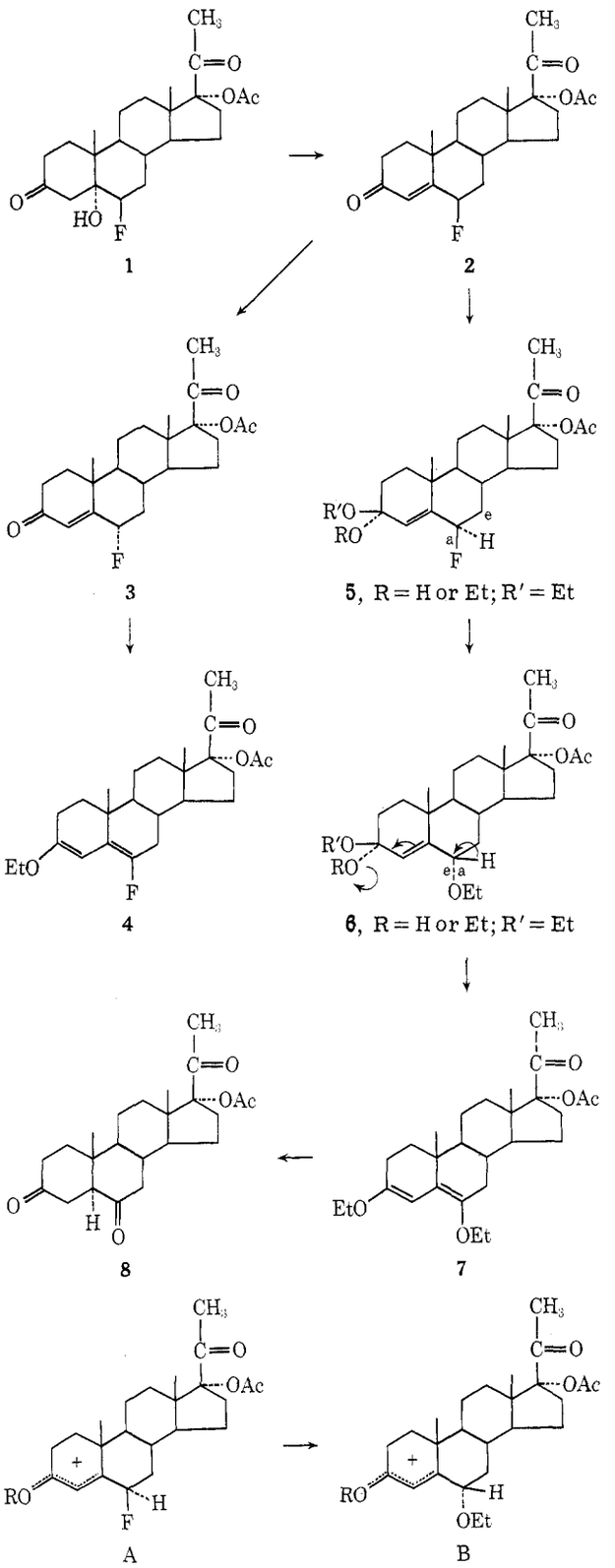
In the course of a series of synthetic transformations, we became interested in the preparation of 3-ethoxy-6-fluoro-17α-acetoxypregna-3,5-dien-20-one (**4**) from 6β-fluoro-17α-acetoxyprogesterone (**2**). Treatment of **2** with triethyl orthoformate in dichloromethane solution in the presence of *p*-toluenesulfonic acid dihydrate at room temperature gave a new compound in 79% yield which differed from the expected dienol ether **4**. The structure of this new compound was established as 3,6-diethoxy-17α-acetoxypregna-3,5-dien-20-one (**7**) based on its physical properties and conversion to the corresponding 3,6-diketone **8** on treatment with acid. Formation of this interesting product may be explained as follows. It is known that 6β-fluoro-3-keto steroids require very severe conditions for epimerization to the corresponding 6α-fluoro isomers, such as treatment with hydrogen chloride in acetic acid for a period of several hours.[2] This indicates that loss of an equatorial



(1) This paper represents Contribution No. 391 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif.

(2) A. Bowers, L. Cuellar Ibañez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).