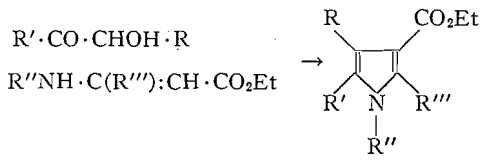
17. C. F. WELLS. Nature, **196**, 770 (1962).
18. G. D. GILES and C. F. WELLS. Nature, **201**, 606 (1964).
19. E. F. CALDIN and G. LONG. J. Chem. Soc. 3737 (1954).
20. E. TOMMILA and J. MURTO. Acta Chem. Scand. **16**, 53 (1962).
21. J. MURTO. Acta Chem. Scand. **18**, 1029, 1043 (1964).
22. A. JOHNSON, B. B. NILAWAR, and R. H. PETERS. Nature, **199**, 692 (1963).
23. R. SCHAAL and F. PEURE. Bull. Soc. Chim. France, 2638 (1963).
24. K. BOWDEN. To be published.
25. B. GUTBEZAHL and E. GRUNWALD. J. Am. Chem. Soc. **75**, 565 (1953). J. E. LEFFLER and E. GRUNWALD. Rates and equilibria of organic reactions. John Wiley and Sons, Inc., New York. 1963. Chap. 8.
26. N. A. IZMAILOV. Proc. Acad. Sci. USSR, Phys. Chem. Sect. English Transl. **127**, 501 (1959).
27. H. S. HARNED and R. A. ROBINSON. Trans. Faraday Soc. **36**, 973 (1949).
28. M. L. DONDON. J. Chim. Phys. 48 (1951).
29. F. MASURE and R. SCHAAL. Bull. Soc. Chim. France, 1141 (1956).
30. R. SCHAAL and A. TEZE. Bull. Soc. Chim. France, 1783 (1961).
31. A. A. MARYOTT and E. R. SMITH. Nat. Bur. Std. (U.S.), Circ. No. 514 (1951).
32. J. T. PINKSTON and H. T. BRISCOE. J. Phys. Chem. **46**, 469 (1942).
33. S. MOURONVAL, R. GABORIAUD, and R. SCHAAL. Compt. Rend. **255**, 2605 (1962).
34. J. R. HOLMES, D. KIVELSON, and W. C. DRINKARD. J. Am. Chem. Soc. **84**, 4677 (1962).
35. G. YAGIL and M. ANBAR. J. Am. Chem. Soc. **85**, 2376 (1963).

RECEIVED JANUARY 26, 1965.
DEPARTMENT OF PURE AND APPLIED CHEMISTRY,
ROYAL COLLEGE OF ADVANCED TECHNOLOGY,
SALFORD, LANCASHIRE, ENGLAND.

THE FEIST SYNTHESIS OF PYRROLE-3-CARBOXYLIC ESTERS

D. M. MCKINNON[1]

In connection with another investigation (1) which required some pyrrole derivatives, their preparation, particularly that of their N-substituted-3-carboxylic esters, was studied. The method of study was that of Feist (2), who condensed benzoin and ethyl β-aminocrotonate in potassium hydrogen sulfate at 170° to produce the N-unsubstituted-pyrrole-3-carboxylic ester (I*a*).

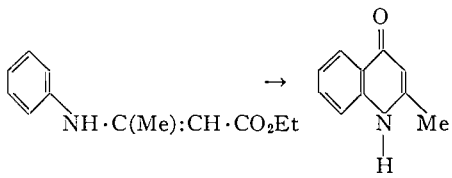


I

	R	R′	R″	R‴		R	R′	R″	R‴
I*a*	Ph	Ph	H	Me	I*i*	H	Ph	CH_2Ph	Me
b	"	"	Ph	"	*j*	"	"	$C_6H_4oNMe_2$	"
c	"	"	C_6H_4oMe	"	*k*	"	"	Me	"
d	"	"	C_6H_4pMe	"	*l*	"	"	H	"
e	"	"	CH_2Ph	"	*m*	Me	Me	Ph	"
f	H	"	Ph	"	*n*	"	"	Me	"
g	"	"	C_6H_4oMe	"	*o*	"	"	H	"
h	"	"	C_6H_4pMe	"	*p*	Ph	Ph	Ph	Ph

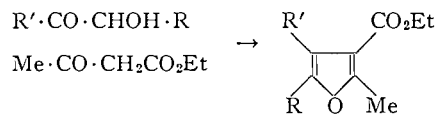
The severe conditions used were inapplicable to the preparation of N-aryl pyrroles, since β-arylaminocrotonic esters cyclize at high temperatures (3), or in strong acid (4), to produce quinolone derivatives (II).

[1]*Dalhousie University Postdoctorate Fellow.*



II

Boiling ethanolic zinc chloride, used previously to condense α-ketols with β-ketoesters, forming furan derivatives (III) (5), also condensed N-substituted and N-unsubstituted



III

crotonic esters, prepared by the reaction of acetoacetic ester with the appropriate amines, with three α-ketols studied, benzoin, α-hydroxyacetophenone, and acetoin, From benzoin and acetoin, the 4,5-diphenyl- (I, *a–e*) and 4,5-dimethyl- (*m–o*) pyrrole-3-carboxylic esters respectively were obtained, while α-hydroxyacetophenone yielded the 4-unsubstituted esters (I, *f–l*) some of which (I, *f–h*, *l*) had been obtained previously (6) by the well-known Paal–Knorr synthesis.

Where it was found impossible to crystallize the pyrrole-3-carboxylic ester, the crude products were either distilled under reduced pressure, or hydrolyzed to the free acid.

Lederer and Paal (6*a*) reported that ethyl α-phenacylacetoacetate condensed with aqueous methylamine to give ethyl 1,2-dimethyl-5-phenylpyrrole-3-carboxylate (I*k*), m.p. 112°. The compound obtained from α-hydroxyacetophenone and ethyl β-aminocrotonate, which gave a satisfactory analysis, had m.p. 75°. Two compounds were obtained from a check of the original experiment. One was identical with that (m.p. 75°) obtained above, while a second, which softened above 85° and melted completely at 112°, was completely converted to the first by being heated at a temperature above its melting point for 5 min. On the basis of its analysis and properties, it is assumed to be an intermediate condensation product (IV), or a tautomer.

$$Ph\cdot CO\cdot CH_2CH(CO_2Et)\cdot C(Me):NMe_2$$

Ethyl β-phenylaminocinnamate also condensed with benzoin under the conditions described above. The tetraphenylpyrrole-3-carboxylic ester (I*p*) was obtained, but the major product was a white crystalline nitrogen-containing material whose infrared spectrum showed no carbonyl absorption. It did not give a satisfactory analysis for any simple product.

The results of the syntheses using α-hydroxyacetophenone show that the groups attached to the carbonyl and hydroxy functions of the α-ketol become pyrrole-5- and pyrrole-4- substituents respectively, and also that the β-aminocrotonic ester must react in that form, and not as its β-iminobutyrate tautomer. They are in contrast to the reactions of α-ketols with β-keto esters (5) where the positions of the substituents in the furans (III) produced are reversed.

These reactions are analogous to the similar Hantzsch (7) and Feist-Benary (8) syntheses of pyrroles and furans where the positions of the group adjacent to the carbonyl function become 5- and 4- substituents respectively.

EXPERIMENTAL

Ethyl β-(o-Dimethylaminophenyl) Aminocrotonate

Equimolar quantities of *o*-aminodimethylaniline and acetoacetic ester, with a trace of acetic acid, were heated under reflux in benzene until the calculated quantity of water, removed by continuous azeotropic distillation, had separated. The solvent was evaporated and the residue distilled under reduced pressure. The pale yellow fraction, b.p. 102° at 0.5 mm was collected (73%).

Found: C, 66.6; H, 7.8; N, 10.3. $C_{14}H_{20}N_2O_2$ requires C, 67.6; H, 8.0; N, 11.3.

2 Methylpyrrole-3-Carboxylic Esters (I, a–o)

Equimolar quantities of the ethyl β-aminocrotonic ester and the α-ketols (acetoin was used as the commercial 85% solution in water) were heated under reflux in ethanol with an approximately equal weight of zinc chloride for times varying between 4 and 24 h. The yellow oils obtained by diluting the ethanol were worked up by trituration under ethanol, distillation under reduced pressure, or hydrolysis to the parent acid. The results are presented in Table I. The products were crystallized from ethanol except where stated.

TABLE I

Preparation of pyrroles from β-aminocrotonic esters and α-ketols

Compound	Reaction time, hours	Yield, %	M.p.	Formula	Required, % C	Required, % H	Required, % N	Found, % C	Found, % H	Found, % N
I*a*	10	42	203–204*	$C_{20}H_{19}NO_2$						
I*b*	24	46	132–134	$C_{26}H_{23}NO_2$	81.8	6.03	3.67	81.5	6.13	3.70
I*c*	24	45†	273‡	$C_{25}H_{21}NO_2$	81.9	5.72	3.82	82.1	5.43	3.58
I*d*	24	68	134	$C_{27}H_{25}NO_2$	81.9	6.32	3.54	81.6	6.51	3.51
I*e*	24	51	126–127	$C_{27}H_{25}NO_2$	81.9	6.32	3.54	82.9	6.72	3.87
I*f*	24	43	92.5–93§	$C_{20}H_{19}NO_2$						
I*g*	24	32	199†,‖	$C_{19}H_{17}NO_2$						
I*h*	24	36	115¶	$C_{21}H_{21}NO_2$						
I*i*	24	54	164	$C_{19}H_{17}NO_2$	78.3	5.83	4.81	77.9	5.68	4.20
I*j*	24	26†	245‡	$C_{20}H_{20}N_2O_2$	75.0	6.25	8.75	74.3	6.69	8.30
I*k*	4	49	74–75**	$C_{15}H_{17}NO_2$	74.1	6.99	5.76	74.3	7.12	6.21
I*l*	4	38	115–116††	$C_{14}H_{15}NO_2$						
I*m*	8	44	—‡‡	$C_{16}H_{19}NO_2$	74.8	7.41	5.45	75.1	7.49	5.97
I*n*	4	38	72–73§§	$C_{11}H_{17}NO_2$						
I*o*	4	46	104–105‖‖	$C_{10}H_{15}NO_2$						

*Lit. (2) 203°.
†As free acid.
‡From acetic acid.
§Lit. (6*a*) 100°. Original experiment repeated gave m.p. 92.5° mixed m.p. 92.5°.
‖Lit. (6*a*) 199°.
¶Lit. (6*a*) 115°.
**Lit. (6*a*) 112°.
††Lit. (6*b*) 115–116°.
‡‡B.p. 142–146°, 0.5 mm.
§§Lit. (6*d*) 72–73°.
‖‖Lit. (6*c*) 104–105°.

Reaction of Ethyl α-Phenacylacetoacetate with Methylamine

The reaction, performed as described (7), afforded a solid precipitate, which was recrystallized from ethanol. It softened at 85° and completely melted at 112°.

Found: C, 68.8; H, 7.01; N, 5.74. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.28; N, 5.57.

The mother liquors of the reaction, diluted with a large excess of water, gave a precipitate, m.p. 75° (from ethanol), which was identical with the pyrrole (I*k*) obtained above. The compound $C_{15}H_{19}NO_3$ obtained above was heated at 120° for 5 min. The cooled product, recrystallized from ethanol, deposited the pyrrole (I*k*), m.p. 75°.

Reaction of Ethyl β-Phenylaminocinnamate with Benzoin

Benzoin and ethyl β-phenylaminocinanmate were heated under reflux with zinc chloride as described above for the 2-methylpyrrole-3-carboxylic ester for 24 h. The mixture, worked up in the usual manner, gave a white solid which was separated into two components by chromatography on activated alumina in benzene. The course of the elution was followed under ultraviolet light. When the first pale fluorescent band had been eluted, the column was stripped with ether.

The first fraction on evaporation yielded a white solid, m.p. 175–176° from ethanol (17.5%).

Found: C, 83.5; H, 5.51; N, 3.29. $C_{31}H_{25}NO_2$ requires C, 83.8; H, 5.66; N, 3.16.

The second fraction on evaporation yielded a colorless crystalline compound, m.p. 212–220° from benzene.

Found: C, 85.5; H, 5.67; N, 6.13.

ACKNOWLEDGMENTS

This work was supported by the Dalhousie University Research and Development Fund for the Sciences.

1. K. T. LEFFEK and D. M. MCKINNON. Unpublished results.
2. F. FEIST. Ber. **35**, 1558 (1902).
3. M. CONRAD and L. LIMPACH. Ber. **20**, 944, 948 (1887).
4. R. G. GOULD and W. A. JACOBS. J. Am. Chem. Soc. **61**, 2890 (1939). C. C. PRICE and R. M. ROBERTS. J. Am. Chem. Soc. **68**, 1204 (1946).
5. F. GARCIA GONZALEZ, F. J. LOPEZ APARICIO, and F. SANCHEY-LAULHE. Anales real Soc. españ. fis. y quim. Madrid, Ser. B, **50B**, 407 (1954); Chem. Abstr. **49**, 13206 (1955). T. SZEKI and E. LASZLO. Ber. **73**, 924 (1940). J. K. N. JONES. J. Chem. Soc. 116 (1945).
6. (*a*) L. LEDERER and C. PAAL. Ber. **18**, 2594 (1885).
   (*b*) V. SPRIO and G. C. VACCARO. Ann. Chim. Rome, **49**, 2075 (1959). Chem. Abstr. **54**, 16443 (1960).
   (*c*) L. KNORR and K. HESS. Ber. **44**, 2762 (1911).
   (*d*) J. L. RAINEY and H. ADKINS. J. Am. Chem. Soc. **61**, 1104 (1939).
7. A. HANTZSCH. Ber. **23**, 1474 (1890). R. C. ELDERFIELD. Heterocyclic compounds. Vol. 1. John Wiley and Sons, Inc., New York. 1950. pp. 132, 290.
8. F. FEIST. Ber. **35**, 1537 (1902). E. BENARY. Ber. **44**, 493 (1911). R. C. ELDERFIELD. Heterocyclic compounds. Vol. 1. John Wiley and Sons, Inc., New York. 1950. p. 132.

RECEIVED OCTOBER 30, 1964.
CHEMISTRY DEPARTMENT,
DALHOUSIE UNIVERSITY,
HALIFAX, NOVA SCOTIA.

STEREOCHEMISTRY OF THE REDUCTION OF CYCLIC KETONES WITH THE PYRIDINE-*n*-BUTYLLITHIUM ADDUCT: STERIC APPROACH AND PRODUCT DEVELOPMENT CONTROLS

R. A. ABRAMOVITCH, W. C. MARSH, AND J. G. SAHA

The dihydropyridyllithium adduct formed from phenyllithium and pyridine has been shown to reduce ketones to the corresponding alcohols (1). While the yield from benzophenone was reasonable (64%), cyclohexanone gave a poor yield (6.5%) of cyclohexanol. It was, nevertheless, thought to be of interest to examine whether or not there was any stereoselectivity in the reduction of cyclic ketones with this reagent. The publication of a study of the stereochemistry of the reduction of cyclic ketones with lithium tri-*t*-butoxyaluminium hydride and the discussion of the factors controlling the geometry of the products formed (2) prompts the reporting of our results.

The reducing agent used here was the adduct (I) formed by the addition of *n*-butyllithium in ether in the cold to an excess of pyridine in dry ether. The ketone in ether was added at room temperature and, after the usual workup (1), the products were analyzed by gas-phase chromatography. In addition to recovered ketone, 2-*n*-butylpyridine was formed, together with the mixture of isomeric alcohols.

Reduction of 4-*t*-butylcyclohexanone in this way gave a mixture of isomeric alcohols of which 91–96% was the *trans*- and 9–4% was the *cis*-isomer. Very similar ratios were obtained when lithium aluminium hydride (3) and lithium tri-*t*-butoxyaluminium hydride (2) were used. It has been proposed (2) that the stereochemical results observed with