authentic sample. The aqueous layer was acidified (hydrochloric acid) and extracted (ether). Evaporation of ether gave 0.41 g (68%) of diphenylacetic acid (13). Recrystallization of 13 from benzene gave colorless granules, mp 147–148 °C. The melting point and IR spectrum of 13 were in good agreement with those of an authentic sample.

Registry No.—1a, 14016-34-3; 1b, 14181-84-1; 1c, 5110-45-2; 1d, 24932-57-8; 2, 151-56-4; *syn*-3a, 61047-06-1; *anti*-3a, 61047-07-2; *syn*-3b, 61047-08-3; *anti*-3b, 61047-09-4; *syn*-3c, 61047-10-7; *anti*-3c, 61047-11-8; 4, 29172-31-4; 5a, 61047-12-9; 5b, 61047-13-0; 5d, 61047-14-1; 6a, 61047-15-2; 6b, 61047-16-3; 7, 61047-17-4; 9, 7495-04-7; 11, 4695-14-1; 14, 4406-41-1; dimethylamine, 124-40-3; diphenylketene, 525-06-4.

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Acid-Catalyzed Addition of Secondary Amines to Cyclopropyl Ketones. Mass Spectra of Some Cyclic Aminobutyrophenones

Joseph Yovell, Daniel Hirsch, and Shalom Sarel*

Department of Pharmaceutical Chemistry, Hebrew University School of Pharmacy, Jerusalem, Israel

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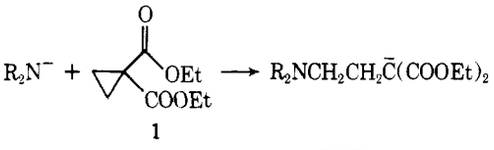
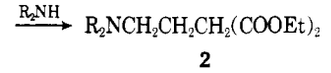
Four cyclic secondary amines [morpholine (**a**), piperidine (**b**), pyrrolidine (**c**), and 2-(1-piperazinyl)ethanol (**d**)] were induced to react with five cyclopropyl ketones of the structure RCO-c-C_3H_5 (**16–20**, R = *p*-anisyl, phenyl, *p*-chlorophenyl, methyl, and cyclopropyl, respectively) in presence of acid to yield ring-opened γ-amino ketones (**21–27**). The products were characterized by their spectroscopic properties (IR, UV, NMR, and MS), derivatives, and other analytical data. The reactivity of the ketones increases in the order cyclopropyl < *p*-anisyl < phenyl < *p*-chlorophenyl. Since this cannot be reconciled with a cyclopropylcarbinyl–homoallylic cation mechanism, the intermediacy of a carbinolamine (**31**) is invoked.

Our studies concerning addition of organomagnesium halides to cyclopropyl ketones,[1] which were accompanied by ring opening, directed our interest to examining the behavior of these ketones toward other nucleophiles such as secondary amines.

Stewart and co-workers[2] have shown that secondary amines add to 1,1-disubstituted cyclopropanes **1** bearing two electron-withdrawing groups in a 1,4 fashion, leading to ring-opened γ-amino esters **2**. The highly conjugated ("bisected")



1



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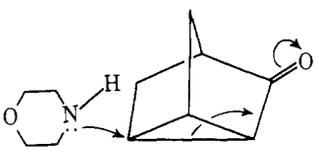
nortricyclanone **3** was shown[3] to add morpholine in a 1,4 manner to give exclusively *exo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**4**), indicating ring rupture by backside nucleophilic attack.

Acid-induced addition of secondary amines to cyclopropanes substituted by carbonyl groups was demonstrated by Cook et al.,[4] who obtained diamino- and aminoimonium salt products (**5** and **6**) from nortricyclanone and pyrrolidine or hexamethylenimine in presence of acids.

The sequence of incorporation of the amines is not known; the role of the catalyst is, apparently, in a dehydration stage.

Direct attack on the carbonyl carbon without ring opening was demonstrated by Cook et al.,[4] on treating nortricyclanone



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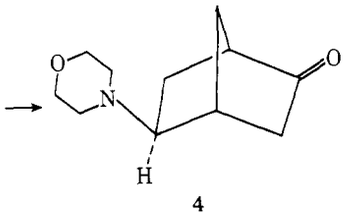

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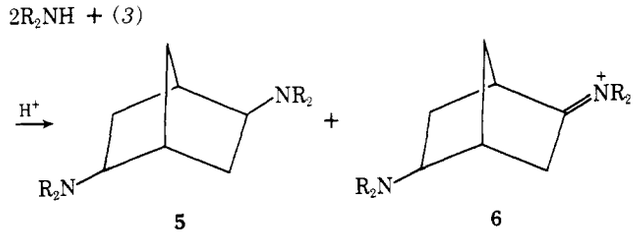
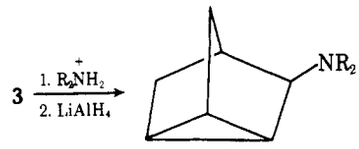


5 6

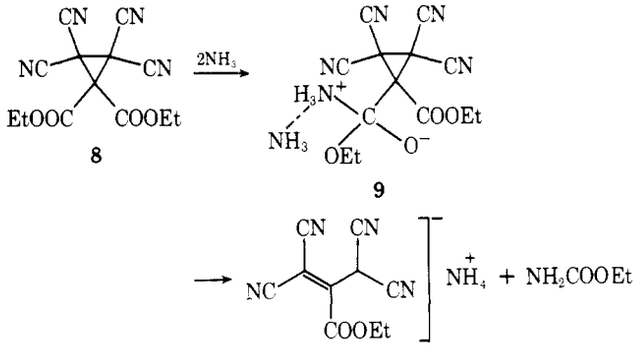
with amine salts rather than with free nucleophilic amines, followed by $LiAlH_4$ reduction (**3** → **7**). They have also obtained[5] ring-retained products from cyclopropanecarboxaldehyde and methyl cyclopropyl ketone in presence of basic and acidic catalysts, respectively.

A rather esoteric reaction of ammonia with 1,1-dicarbethoxy-2,2,3,3-tetracyanocyclopropane (**8**) was reported by Regan.[6] Although the ring becomes highly deficient of elec-



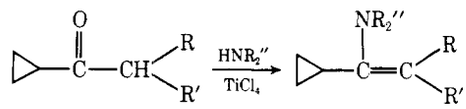
7

trons due to *six* electron-withdrawing groups, the nucleophilic attack occurs initially at the carbonyl group. The emerging carbinolamine (**9**) collapses with ring opening by intramolecular Michael type addition to yield ammonium 2-carbethoxy-1,1,3,3-tetracyano-2-propenide (**10**):



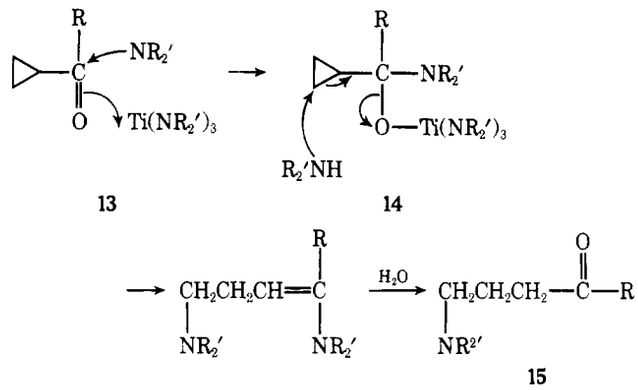
8 9 10

Recently, Pocar and his collaborators[7] have demonstrated two modes of reaction between secondary amines and cyclopropyl ketones under the influence of $TiCl_4$. Ketones possessing α hydrogen other than cyclopropyl methinic (**11**) gave enamines with ring retention (**12**):



11 12

Ketones lacking enolizable protons (**13**) yielded γ-amino ketones by the route portrayed below:



13 14 15

Our study concerns structural factors influencing yields of open-chain products resulting from addition of cyclic secondary amines (**a–d**) to alkyl and aryl cyclopropyl ketones (**16–20**) in presence of proton acid. The reaction conditions and products were virtually uniform: a mixture of the ketone, slight excess of the amine, and 10 mol % *p*-TsOH was boiled for 20–30 h neat or with toluene or xylene as diluent, yielding γ-amino ketone (**21–27**) as the sole product.

The products were isolated by vacuum distillation or crystallization and freshly purified by GLC for the analytical and spectral measurements, since they darken on aging (Table I).

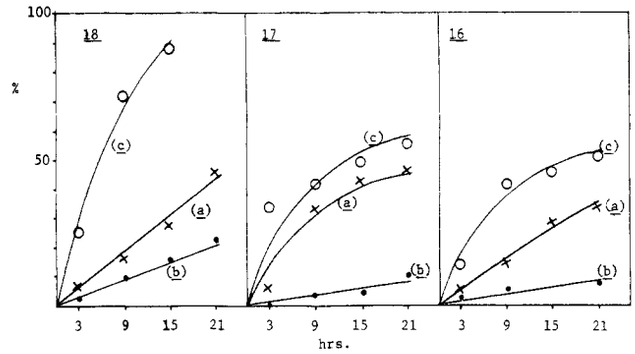
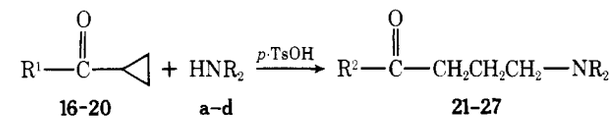


Figure 1. Consumption of aryl cyclopropyl ketones by addition of secondary amines. Ketone:amine:*p*-TsOH 1:1.3:0.1; external temperature 120–125 °C.

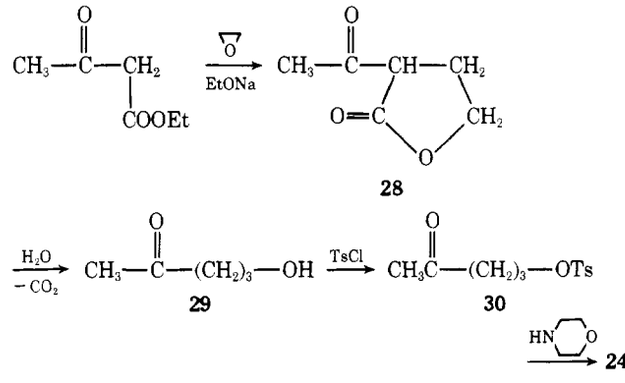


16-20 a–d 21-27

16, **21**, $R^1 = R^2$ = *p*-anisyl
17, **22**, $R^1 = R^2$ = phenyl
18, **23**, $R^1 = R^2$ = *p*-chlorophenyl
19, **24**, $R^1 = R^2$ = methyl
20, **25**, $R^1 = R^2$ = cyclopropyl
26, R^2 = 3-morpholinopropyl
27, R^2 = *p*-hydroxyphenyl

a, HNR_2 = morpholine
b, HNR_2 = piperidine
c, HNR_2 = pyrrolidine
d, HNR_2 = 2-(1-piperazinyl)ethanol

Elemental analysis of the free amino ketones and their respective picrate salts (Table III) and molecular weight determination by mass spectrometry of the latter[8] show that the products are 1:1 adducts (except **26a**, where dicyclopropyl ketone added two molecules of morpholine, one to each of the rings). The $R^1C{=}O$ portions of the starting ketones are retained in the products (**26a** and **27a** excluded) as evidenced by the carbonyl stretching vibration absorption (1676–1701 cm^{-1} for the aromatic ketones and 1710–1735 cm^{-1} for the aliphatic ones) and UV absorption bands (λ_{max} 241–242, 251–252, and 272–275 nm for phenyl, *p*-chlorophenyl, and *p*-anisyl ketones, respectively) detailed in Table II. Cyclopropyl signals are absent in the NMR spectra (Table II; **25a** is an obvious exception) and are replaced by three new methylene signals—a triplet for the methylene α to carbonyl, a quintuplet for the β-CH_2 group,[13] and a signal for the methylene bonded to nitrogen appearing with those of the amine and revealed by integration. The structures were further substantiated by some derivatizations (hydrochlorides of **22d** and **26a**, methiodides of **24a** and **26a**, deuteration of **21a**, carbinols from **24a** by $LiAlH_4$ reduction and from **21a**, **21c**, and **22a** by Grignard addition; see Table III) and by independent alternative synthesis of **24a** as follows:



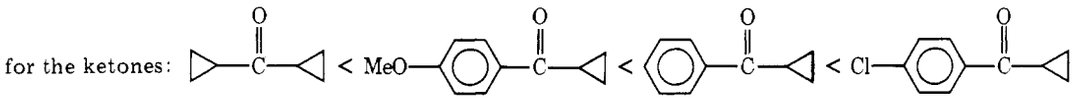
28 29 30 24a

Table I. Analytical Data of γ-Amino Ketones[j]

γ-Amino ketone	Method[a]	Yield[b]	Bp, °C (mmHg) or mp, °C	n^{25}D	Mol wt[c]
21a	C	55	55–56[h]		263
21b	A	40	125 (0.6)	1.5562	261
21c	A	43	164–169 (0.9)	1.5483	247
21d	B	27	87–88		306
22a	A	65	139–141 (0.3)[h]	1.5346	233
22b	A	26	132–136 (0.7)[e]	1.5361[e]	231
22c	A	58	154–160 (3.6)	1.5369	217
22d	D	64	83–84		276
23a	A, B	26	160–165 (0.6)[h]	1.5305	267
23b	A	50	152–155 (0.8)[f]	1.5317	265
23c	B	42	64–65[g]		251
23d	B	51	73–74		310
24a	A	55	72–73 (0.4)[d]	1.4615[d]	171
25a	E	11	120–122 (2.0)	1.4795	197
26a	E	28	178–180 (0.8)	1.4875	284
27a	C	2.5	172–173		249[i]

[a] See Experimental Section. [b] Percent of isolated material. [c] By MS of the corresponding picrate.[8] [d] Lit.[9] 81 °C (0.5 mm); n^{24}D 1.4630. [e] Lit.[10] 144–146 °C (3 mm); n^{20}D 1.5348. [f] Lit.[11] 148–150 °C (0.25 mm). [g] Lit.[11] 58–60 °C. [h] Reported in the literature[12] as HCl salt. [i] By MS of the free base. [j] Satisfactory analytical data (±0.4% for C, H, N) for all new compounds were submitted for review.

The yields listed in Table I relate to the amounts of isolated products, not to those actually formed. Estimation of the relative reaction rates could be determined from experiments run in parallel under identical conditions of concentration, temperature, and duration, following the consumption of the starting ketone by GLC analysis.[14] The results of such study at 120–125 °C are represented graphically in Figure 1; dicyclopropyl ketone (**20**) is not represented because it was totally inactive toward all the amines under these conditions, which are ca. 25 °C lower than the preparative reflux temperature. Two sequences of the relative reactivities can be deduced from the data:



for the amines: piperidine < morpholine < pyrrolidine

The order in the ketone series cannot be reconciled with a cyclopropylcarbinyl–homoallylic cation mechanism. Initial formation of a cation $R^+C(OH)$-c-C_3H_5 by protonation of the ketone should be enhanced by electron-donating R groups and hampered by electron-withdrawing ones,[15] contrary to the order observed. The order observed reflects an increase in the electrophilicity of the carbonyl carbon atom on going along the series from cyclopropyl to *p*-chlorophenyl, suggesting initial attack of the amine at this site rather than at the ring, to form a carbinolamine (**31** in Scheme I).

In the amine series the lower tendency of piperidine ($K = 1.6 \times 10^{-3}$) to react with ketones as compared with that of the

Table II. Spectral and NMR Data of γ-Amino Ketones

Registry no.	Compd	$\nu_{C=O}$, cm^{-1}	λ_{max}, nm (log ε) (in EtOH)	τ (*J*, Hz),[d] O=CCH$_2$(t)	CH$_2$N (m)	CH$_2$CH$_2$CH$_2$ (q)
5170-66-1	**21a**[c]	1686[b]	274 (4.19)	7.05 (7.0)	7.46–7.70	8.08 (7.0)
61025-28-3	**21b**	1695[a]	275 (4.22)	7.07 (7.0)	7.33–7.75	8.09 (7.0)
61025-29-4	**21c**	1701[a]	273 (4.12)	7.03 (6.7)	7.30–7.70	8.07 (6.7)
37133-86-1	**21d**	1676, 3415[b,c]	272–273 (4.23)	7.05 (6.5)	7.28–7.75	8.10 (6.5)
3935-01-1	**22a**	1701[a]	242–243 (4.06), 280 (3.01)	6.99 (7.0)	7.38–7.74	8.06 (7.0)
4476-25-9	**22b**	1695[a]	242–243 (4.14), 279 (3.03)	7.04 (7.0)	7.40–7.80	8.10 (7.0)
59921-83-4	**22c**	1695[a]	242 (4.06), 279 (3.04)	6.97 (7.0)	7.30–7.65	8.06 (7.0)
61025-30-7	**22d**	1687, 3415[b,c]	241 (4.14), 278 (3.17)	6.99 (6.5)	7.32–7.70	8.06 (6.5)
5487-31-0	**23a**	1689[a]	252 (4.22)	6.98 (7.0)	7.40–7.75	8.09 (7.0)
2888-40-6	**23b**	1686[a]	252 (4.20)	7.05 (7.0)	7.45–7.80	8.08 (7.0)
2895-68-3	**23c**	1672[b]	252 (4.18)	7.00 (7.0)	7.30–7.70	8.06 (7.0)
61025-31-8	**23d**	1685, 3415[b,c]	251 (4.22)	7.04 (7.0)	7.34–7.72	8.07 (7.0)
59127-81-0	**24a**	1735[a]		7.35–7.80		8.25 (7.0)
61025-32-9	**25a**	1710[a]		7.25–7.82		7.92–8.42
61025-33-0	**26a**	1730[a]		7.30–7.75		8.20 (7.0)
61025-34-1	**27a**[f]	1681, 3400[b,c]	280–281 (4.26)	7.13 (7.0)	7.63–7.93	8.27 (7.0)

[a] Neat. [b] In KBR. [c] ν_{OH}, broad. [d] 60 MHz in $CDCl_3$, Me_4Si; d = doublet; t = triplet; q = quintuplet; s = singlet; m = multiplet. Other signals appear as follows. Aromatic protons: *p*-$MeOC_6H_4$, $A_2'B_2'$ centered at τ 2.55–2.60 with $\Delta\nu_{AB} \sim 60$ Hz; C_6H_5, m at τ 1.90–2.17 and 2.36–2.77; *p*-ClC_6H_4, $A_2'B_2'$ centered at τ 2.30–2.35 with $\Delta\nu_{AB} \sim 30$ Hz. Cyclic CH_2 not adjacent to N: morpholine, A_2' of $A_2'X_2'$ at τ 6.10–6.52; piperidine, broad single band at τ 8.26–8.82; pyrrolidine, m at τ 8.10–8.41; CH_3O, s at τ 6.13–6.20; CH_2OH, t at τ 6.36–6.39 (*J* 5.0 Hz); CH_2CO, s at τ 7.84; cyclopropyl CH_2, m at 8.92–9.31; cyclopropyl CH, m at 7.92–8.42. [e] 100-MHz NMR. [f] NMR in Me_2SO-d_6.

Scheme I

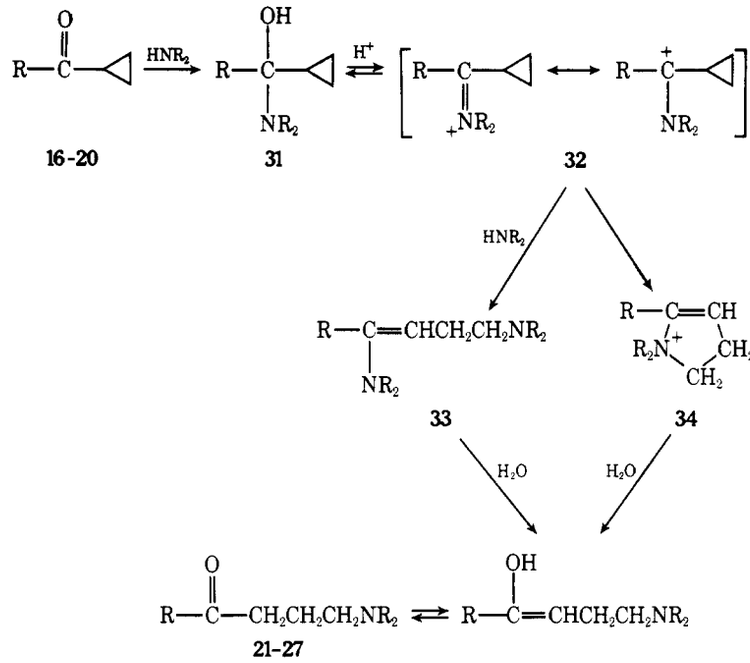


Table III. Derivatives of γ-Amino Ketones[k]

Registry no.	Derivative[a]	Mp, °C	NMR, τ[b]
61025-35-2	**21a** picrate	169–171	
61025-36-3	**21a**-d_2[c]		7.46–7.70 (m, 6 H), 808 (6, J = 7.0 Hz, 2 H)[d]
61062-59-7	**21b** picrate	128–129	
61025-37-4	**21c** picrate	139	
61025-38-5	**21d** dipicrate	238	
61025-39-6	**22a** picrate	140	1.24 (s, 2 H), 5.85–6.00 (A_2' of $A_2'X_2'$, 4 H), 6.18–6.50 (m, 2 H), 6.60–6.96 (m, 6 H), 7.80 (q, J = 7.0 Hz, 2 H)[d]
61025-40-9	**22b** picrate	127	
61025-41-0	**22c** picrate	104–105	
61025-42-1	**22d** dipicrate	215–216	
61025-43-2	**22d** 2HCl[e]	231	
61025-44-3	**23a** picrate	188–190	
61025-45-4	**23b** picrate	153–154	
61025-46-5	**23c** picrate	158	
61025-47-6	**23d** dipicrate	236 dec	
61025-48-7	**24a** picrate	132–133	
61025-49-8	**24a** HCl[f]	155–156	5.95–6.20 (A_2' of $A_2'X_2'$, 4 H), 6.60–7.10 (m, 6 H), 7.32 (t, J = 6.8 Hz, 2 H), 7.89–8.41 (m, 2 H)[g]
61062-60-0	**24A** MeI[h]	110–111	
61025-50-1	**24a** OH[i]		4.95 (s, 1 H), 6.08–6.48 (m, 5 H), 7.30–7.80 (m, 6 H), 8.13–8.65 (m, 4 H), 8.86 (d, J = 6.8 Hz, 3 H)
61025-51-2	**24a** OH MeI[h]	141	
61025-52-3	**25a** picrate	57–59	
61025-53-4	**26a** dipicrate	199	
61025-54-5	**26a** 2HCl	231	5.80–6.20 (m, 8 H), 6.36–7.03 (m, 12 H), 7.32 (t, J = 6.8 Hz, 4 H), 7.67–8.33 (m, 4 H)[g]
61025-55-6	**26a** 2MeI[h]	256–257	
61025-56-7	**37**	98	2.83 ($A_2'B_2'$, $\Delta\nu_{AB} \sim 35$ Hz, 4 H), 2.33–2.87 (m, 5 H), 6.23 (s, 3 H), 7.39–7.81 (m, 8 H), 8.16–8.60 (m, 2 H)
61025-57-8	**38**	123–124	2.53–3.50 (m, 8 H), 6.29 (s, 3 H), 7.45–7.88 (m, 8 H), 8.20–8.63 (m, 2 H)
972-05-4	**39**	117–118[j]	2.20–2.80 (m, 10 H), 7.45 (t, J = 6.0 Hz, 2 H), 7.50–7.76 (m, 6 H), 8.34 (q, J = 6.0 Hz, 2 H)
61025-58-9	**40**	145	2.48–3.38 (m, 8 H), 6.29 (s, 3 H), 7.33–7.87 (m, 8 H), 8.08–8.62 (m, 6 H)

[a] Experimental Section for methods of preparation and crystallization. [b] For experimental conditions, notation, and signals missing in the tabulated spectra, refer to Table II and footnote *d* therein. [c] 4′-Methoxy-4-morpholino-2,2-dideuteriobutyrophenone. [d] 100 MHz. [e] Prepared by method D. [f] Hygroscopic. [g] In D_2O/TSP. [h] Methiodide. [i] Methyl-3-morpholinopropylcarbinol by $LiAlH_4$ reduction of **24a** in dry THF; 70% yield, bp 82–83 °C (0.3) mm, $n^{28}D$ 1.4685. [j] Lit.[23] 128–130 and lit.[24] 123 °C. [k] Satisfactory analytical data (±0.4% for C, H, N, and halogen) for all compounds, except as noted, were submitted for review. Exceptions [found (calcd)]—**22d** 2HCl: C, 55.50 (55.01); H, 6.90 (7.45); N, 7.58 (8.02); Cl, 19.81 (20.30). **23c** picrate: C, 50.42 (49.95); H, 4.82 (4.40). **25a** picrate: C, 47.38 (47.88). **26a** dipicrate: C, 43.16 (43.68); H, 4.09 (4.58). **26a** 2HCl: C, 50.91 (50.42); H, 8.76 (8.40); N, 7.38 (7.84); Cl, 20.30 (19.89).

equally basic pyrrolidine ($K = 1.3 \times 10^{-3}$) finds analogy in enamine chemistry.[16] It can be attributed to the acid-induced dehydration stage of the carbinolamine (**31** → **32**). This conversion entails rehybridization of the nitrogen atom orbitals from tetrahedral to trigonal, which is faster in the five-membered than in the six-membered cyclic amine.

The collapse of the imonium–carbonium mesomeric ion (**32**) can occur by two different pathways, both having analogies in the literature. Ion **32** can undergo homoallylic rearrangement concomitant with attack of a second amine molecule to yield γ-aminoenamine (**33**). Similar products were reported recently from reactions with $TiCl_4$ catalyst.[7] The hydrolysis of **33** to the final product is now straightforward. An alternative route worthy of consideration involves the cyclopropyl ketimine–pyrroline rearrangement. This rearrangement has been shown to proceed with enhanced rate in acid medium, where the ketiminium form, such as **32**, is the active species.[17] This route has been advantageously exploited recently in synthesis of alkaloids.[18] In the cases reported here, the rearrangement should give rise to pyrrolinium ions (**34**) which easily hydrolyze to the products.

The formation of the bis adduct **26a** is the result of addition of morpholine to the mono adduct **25a**. The product **27a** was obtained in low yield from the reaction of **16** with morpholine by hydrolysis of the methyl ether function during the long boiling period, either at the starting ketone **16** or at the product **21a**.

Some of the amino ketones produced in this study were previously shown to possess biological activity as psychotropic[12b,19] or antihypertensive[20] agents. The synthetic method described here provides an easy and convenient access to this class of compounds.

Mass Spectra. Fragmentation paths of amino ketones under electron impact are classified according to the alleged triggering site—amine-directed decompositions and carbonyl-directed ones. Interpretation of the fragmentation patterns must take into account not only the distribution of "localized" charge between the sites but also the relative rates of the various decompositions. Wagner[20] applied the standard unimolecular decay law for kinetic analysis of the charge distribution in γ-dimethylaminobutyropheone (DMAB) as compared to separate amine and ketone model compounds, and demonstrated clearly the predominance of charge residence at the nitrogen. Extending Wagner's treatment to the compounds produced in the present work brings forth the question of mutual influence of the two ionizable centers as a function of either changes in the amine or in the ketone portions of the molecule. We shall confine our discussion here to the different amines when attached to unsubstituted butyrophenone.

The three most prominent cracking processes are depicted in Scheme II, their intensities under 70 eV are assembled in Table IV, and their relative kinetic parameters are assembled in Table V.

Scheme II

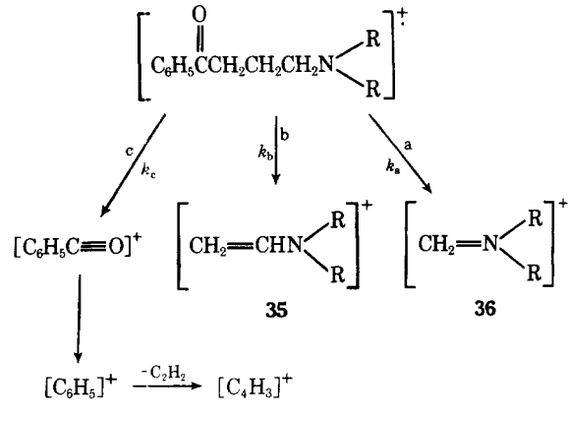


Table IV. Major Intensities in Mass Spectra of Some γ-Aminobutyrophenones

m/e	DiMe amine DMAB[e]	Pyrrolidine 22c	Piperidine 22b	Morpholine 22a
51[c]	265	220	55	145
58	4350[a]			
71	3130[b]			
77[c]	630	530	270	525
84		4240[a]		
97		2800[b]		
98			1750[a]	
100				2285[a]
105[c]	340	440	285	580
111			1450[b]	
113				1830[b]
120	15	20	20	110
191	100[d]			
217		100[d]		
231			100[d]	
233				100[d]
total intensity $\left(\sum_{40}\right)$	12 000	17 530	8370	12 000

[a] α to nitrogen cleavage (route a in Scheme II), base peak. [b] McLafferty rearrangement with charge residing on the amine portion (route b in Scheme II). [c] Benzoyl ion and ions of its further decomposition. [d] Molecular ion. [e] Data from ref 21.

Table V. Relative Kinetic Constants for Major Fragmentation Processes of γ-Amino Ketones

	DMBA	22c	22b	22a
k_a	1.9	1.4	1.0	1.0
k_b	1.7	1.1	1.0	1.0
k_c[a]	1.5	1.1	1.0	1.5
$[M^+]/\sum_{40}$	1.5	1.0	2	1.5

[a] Figured from the sum of the intensities of peaks at m/e 105, 77, and 51.

A twofold increase in the abundance of the molecular ion is noticed upon going from pyrrolidino to morpholino and dimethylamino to piperidino ketone. This implies that the tendency of the molecular ion to fragment is affected by a variety of factors, suggesting a considerable degree of charge delocalization in the ionized amino ketones. The higher rate of α to nitrogen cleavage (k_a) in DMAB and **22c** may be attributed to the higher stability of the product, the iminium ion **36**, in parallel to solution chemistry. The significant differences in the values of k_c may indicate proximity of the amine and the carbonyl, while those of k_b draw distinction between the open-chain and the cyclic amines.

Experimental Section

Materials. Commercial cyclopropyl ketones and p-TsOH–H_2O were used without further purification. Commercial amines were freshly distilled from KOH.

Instrumentation. All melting points are uncorrected and recorded as observed on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were taken on a Zeiss spectrophotometer PMQ II. Proton magnetic resonance spectra were determined in deuteriochloroform with Me_4Si internal standard on either Varian A-60 or JEOL GNM-C-60H (60 MHz) and Varian HA-100 (100 MHz) spectrometers. Mass spectra were recorded on a Varian MAT CH-5 spectrometer. Gas–liquid chromatography was performed on a Varian Aerograph Model A-90-P3 gas chromatograph (thermal

conductivity detector) with the following columns: column A, 2 ft × 0.25 in., 10% of 4:1 Apiezon L–KOH on 60/80 Chromosorb W at 240 °C and 40 ml/min He flow rate, for identification and comparison; column B, 5 ft × 0.25 in., 10% cyanosilicone XF-1150 on 30/60 Chromosorb W, with He flow of 30 ml/min and suitable temperature in the range 220–270 °C, for preparative purification.

General Methods for Addition of Secondary Cyclic Amines to Cyclopropyl Ketones. Method A. A mixture of cyclopropyl ketone (0.1 mol), amine (0.13–0.15 mol), and *p*-TsOH (0.01 mol) is refluxed for ca. 20 h, cooled, and poured into 100–150 ml of ether. The precipitated amine tosylate is filtered off, and the filtrate dried over anhydrous $MgSO_4$ and distilled. The products darken on storing in the refrigerator. Pure samples for analytical and spectroscopic measurements were obtained freshly by GLC.

Method B. A mixture of cyclopropyl ketone (50 mmol), amine (50–75 mmol), *p*-TsOH (5 mmol), and 10–15 ml of toluene is refluxed for 20–30 h, then poured into 100–150 ml of 5% HCl. The mixture is extracted with 200 ml of ether. The ethereal solution is dried over anhydrous $MgSO_4$ and evaporated to dryness under vacuum. The crude product is purified by crystallization from benzene.

Method C. Reaction of *p*-Anisyl Cyclopropyl Ketone (16) with Morpholine (a). Method A is applied with the following changes: The final ethereal solution is concentrated to ca. 10–15 ml and allowed to stand for 24 h. **27a** separates and is filtered. The remaining solvent is removed in vacuo from the filtrate, the residue dissolved in a few milliliters of acetone, and **21a** precipitated by cooling in dry ice–acetone mixture.

Method D. Reaction of Phenyl Cyclopropyl Ketone (17) with 1-(2-Hydroxyethyl)piperazine (d). Method B is applied with the following change: on pouring the reaction mixture into 5% HCl the di-HCl salt of the addition product (**22d**) separates and is filtered and twice recrystallized from alcohol. The free base is obtained by dissolving the salt in 40% NaOH, extracting with chloroform, evaporating to dryness, and crystallizing from benzene.

Method E. Dicyclopropyl ketone (**20**, 5.5 g, 50 mmol), 5.5 g (63 mmol) of dry morpholine, and 0.86 g (5 mmol) of *p*-TsOH in 50 ml of xylene (dried over Na) were refluxed for 15 h. After cooling some precipitated morpholine tosylate was filtered, the filtrate boiled with charcoal and refiltered, the solvent removed under vacuum (hot water bath, 1 mm), and the residue fractionated.

Alternative Synthesis of 24a. 1. α-Acetyl-γ-butyrolactone (**28**) was prepared by condensing ethyl acetoacetate with ethylene oxide (NaOEt catalyst).[22]

2. Methyl 3-hydroxypropyl ketone (**29**) was prepared by hydrolysis and decarboxylation of α-acetyl-γ-butyrolactone with 5% H_3PO_4.[23]

3. Methyl 3-tosyloxypropyl ketone (**30**) was prepared by the method of Tipson.[24] Separate solutions in dry pyridine of **29** (10 g in 30 ml) and *p*-TsCl (21 g in 70 ml) were cooled in an ice–salt bath, then mixed and kept in the cooling bath for 2 h. Water (110 ml) was added in portions keeping the temprature below 5 °C. The mixture was extracted with three 100-ml portions of chloroform and the extract washed successively with ice-cold dilute H_2SO_4, water, and sodium bicarbonate solution. After drying (anhydrous Na_2SO_4) the solvent was removed under vacuum (without heating) and the oily residue [ν (SC) 1730 (C=O), 1380 and 1190 cm^{-1} (tosyl ester)] was used without further purification.

4. 24a was prepared according to Reynolds and Kenyon.[25] The crude tosyl ester **30** was added dropwise into a slight excess of stirred dry morpholine. Stirring was continued for 30 min and the excess amine removed under vacuum, causing the mixture to solidify. The mixture was dissolved in hot dry benzene, and on cooling, *p*-TsOH separated and was filtered off. The product was obtained from the filtrate by distillation.

Preparation of Derivatives. Picrates were prepared and recrystallized from alcohol.

Hydrochlorides were prepared by passing HCl through an ethereal solution of the substrate and crystallizing the precipitate from MeOH–Et_2O mixture.

Methiodides were prepared by warming with excess MeI and crystallizing as follows: **24a** MeI, by dropwise addition of *n*-BuOH to the cooled and stirred solution in MeOH; **26a** MeI, by Soxhlet extraction with MeOH; **24a** OH MeI, by trituration in Et_2O.

Deuteration was performed by dissolving in >98% D_2O and the minimal required amount of trifluoroacetic acid, allowing 48 h at room temperature, adding solid NaOH to alkalinity, extracting with ether, and isolating by GLC. Two such cycles complete the exchange

Grignard Addition. A solution of 20 mmol of ketone in 50 ml of dry ether is added dropwise to a solution of 40 mmol of Grignard reagent in ether. The mixture is refluxed for 30 min and hydrolyzed slowly with 10 ml of saturated NH_4Cl solution. The organic layer is decanted and the residue extracted by warming with additional ether. The combined etheral solution is dried ($MgSO_4$), concentrated, and allowed to stand. The separated crystalline carbinol is filtered and washed with a little cold ether. The following compounds were prepared by this method: *p*-anisylphenyl-3-morpholinopropylcarbinol (**37**), from **21a** and C_6H_5MgBr; *p*-anisyl-*p*-chlorophenyl-3-morpholinopropylcarbinol (**38**), from **21a** and *p*-ClC_6H_4MgBr; diphenyl-3-morpholinopropylcarbinol (**39**), from **22a** and C_6H_5MgBr; *p*-anisyl-*p*-chlorophenyl-3-(1-pyrrolidinyl)propylcarbinol (**40**), from **21c** and *p*-ClC_6H_4MgBr.

Registry No.—**16**, 7152-03-6; **17**, 3481-02-5; **18**, 6640-25-1; **19**, 765-43-5; **20**, 1121-37-5; **a**, 110-91-8; **b**, 110-89-4; **c**, 123-75-1; **d**, 103-76-4; C_6H_5Br, 108-86-1; *p*-ClC_6H_4Br, 106-39-8.

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(14) Only three signals appear in the chromatogram throughout the process—amine, ketone, and amino ketone. The second is the most convenient to integrate, and this eliminates the need to account for differences in the specific detector responses to the various products. The ketone alone, heated similarly, is not consumed. Changes in the chromatographic conditions were corrected by repeated comparison of the reacted mixture with an unreacted sample. The results were reproducible within ±3%.
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